Predictors of mortality and survival in type 1 diabetes: a retrospective cohort study of type 1 diabetes mellitus (T1D) in the Wirral Peninsula

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Predictors of mortality and survival in type 1 diabetes: a retrospective cohort study of type 1 diabetes mellitus (T1D) in the Wirral Peninsula

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Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or another institute of learning.

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Abstract

Predictors of mortality and survival in Type 1 diabetes: A retrospective cohort study of Type 1 Diabetes Mellitus (T1D) in the Wirral Peninsula

Background: The prevalence of T1D is rising, despite improvements in the management of this condition. It presents a risk of premature and excess mortality, which impacts survival and life expectancy.

Aim: The study aim was to assess mortality, identify predicting risk factors for mortality and survival in T1D in the Wirral. A systematic review was done to establish present current evidence of all-cause and cause-specific mortality amongst T1D patients.

Methods: A retrospective cohort study design, 1786 patients diagnosed with T1D extracted from the Wirral Diabetes Register (WDR). The follow-up period was between 1st of January, 2000 to 31st December, 2012. The primary outcome measured was all-cause mortality.

R**esults:** 1458 participants with T1D meet the inclusion criteria, after a follow-up period of 12 years, 113(7.75%) deaths were recorded. While the incidence rate was steady over the study period, the prevalence rate continued to increase over the study period.

Significant predictors of mortality in this cohort were age of diagnosis, duration of diabetes, $HbA_{1c,}$ systolic blood pressure (SBP), diastolic blood pressure (DBP), and triglyceride levels. The predicting risk gender, age at diagnosis, duration of T1D, BMI, serum creatinine levels, SBP, total cholesterol, LDL, HDL, TC\HDL, and LDL\HDL showed a linear increase in mortality risk. IMD and DBP followed a U-shaped relationship with relative and absolute mortality, while HbA1c levels reveal a sinusoidal pattern with the highest risk of mortality at the levels ≤ 5.9% (41 mmol/mol). The risk of mortality for the predicting risk factors for this study ranged between 5% and 9%. Maximal risk of mortality of 9% was recorded in the predicting risks of smoking, BMI, SBP, and DBP. The risk of mortality of 8% was recorded for IMD, serum creatinine, total cholesterol, TG, LDL\HDL ratio, and TSH. The risk of mortality of 7% was recorded for the predicting variables of HbA1c, HDL, LDL, and TC\HDL ratio. The minimum risk of mortality of 5% was recorded for the predictor variable of the duration of diabetes. The significant predictors of mortality were the age at diagnosis, duration of diagnosis, systolic and diastolic blood pressure, $HbA_{1c.}$ The burden of mortality rest disproportionately with females who had higher relative risk of mortality of 4 times that of their male counterparts, however, the burden of premature mortality as recorded by the years of potential life lost was slightly higher in males (1797[53.6%]) as compare to females (1553[46.4%]). Of the 113 deaths recorded for the cohort that indicated a proportion of 7.75% of the total T1D patients, records for only 37 participants were retrieved. The principal cause of death in this cohort was malignancy-related 8 deaths (21.6%), this was followed by cardiovascular disease and sepsis, each having 6 deaths (16.2%) respectively. Cerebrovascular disease accounted for 5 deaths (13.5%). Death from diabetes complications (hypoglycaemia) was recorded in 1 patient (2.7%). There were marked reductions in life expectancy for this cohort. Life expectancy at 40 years for females was to an average age mortality of 66.2 years as compared to males 78.3 years. There has been improved survival for T1D in this cohort, 77.185 years [95% CI: 75.191 – 79.179] in males and 76.011 years [95% CI: 73.169 – 78.000] in females.

The systematic review highlighted increased mortality in those with T1D as compared to the general population, females showed greater risk of vascular complications as compared to the males with T1D. 35 studies were included. Results showed all-cause mortality RR 3.73 (95% CI 3.19, 4.36) compared to general population, with gender specific mortality RR 1.17 (95% CI 1.06, 1.29). For cause specific mortality risk (overall and gender specific): cardiovascular

disease RR 3.48 (95% CI 3.14, 3.86) and RR 1.41 (95% CI 0.92, 2.17); renal disease RR 1.06 (95% CI 0.89, 1.26) and RR 0.63 (95% CI 0.38, 1.04); neoplasms RR 1.03 (95% CI 0.92, 1.16) and RR 1.18 (95% CI 0.75, 1.86); cerebrovascular disease according to gender RR 0.99 (95% CI 0.66, 1.48), and accidents and suicides according to gender RR 2.30 (95% CI 1.31, 4.06).

Conclusion

In conclusion, the study highlighted significant mortality risk in females as compared to their male counterparts; there has been progress in the survival of patients with T1D. However, life expectancy remains reduced as compared to those without the condition. Prevalence of T1D continues to increase, and the complex interplay of the predictor variables support the need for an individualised approach to care.

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List of Abbreviations

ACE inhibitor Angiotensin-converting-enzyme inhibitor

ADA American Diabetes Association

AITD Autoimmune thyroid diseases

AMI acute myocardial infarction

CAD Coronary artery disease

CHD Coronary artery disease

CVD Cardiovascular disease

CYP Children and young people

DAFNE Dose Adjustment for Normal Eating programme

DBP Diastolic blood pressure

DCC/EDIC Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group

DESMOND Diabetes education and self-management for ongoing and newly diagnosed

DKA Diabetic ketoacidosis

DN Diabetic nephropathy

DR Diabetic retinopathy

EPR Electronic patient health record

ESRD End stage renal disease/failure

FPG Fasting plasma glucose

GADA Glutamic Acid Decarboxylase Autoantibodies

GDM Gestational diabetes

GRS Genetic risk scores

HbA_{1c} Glycated haemoglobin

IA-2A Insulinoma-Associated-2 Autoantibodies

IAA Insulin Autoantibodies

ICA Islet Cell Cytoplasmic Autoantibodies

IDF International Diabetes Federation

IMD Index of multiple deprivations

JDRF Juvenile Diabetes Research Foundation

JSNA Wirral Joint Strategic Needs Assessment

LDL Low density lipoproteins

LGA large for gestational age babies

MODY Maturity onset diabetes of the young

NICE National Institute for Health and Clinical Excellence

NSF National Service Framework

OGTT oral glucose tolerance test

ONS Office of National Statistics

PAD peripheral artery disease

PVD peripheral vascular disease

RPG Random plasma glucose

T1D Type 1 diabetes

T2D Type 2 diabetes

TSH Thyroid stimulating hormone

UK United Kingdom

WDR Wirral Diabetes Register

WHO World Health Organisation

WHR Waist-to-hip ratio

X-PERT The Diabetes X-PERT Programme

ZnT8 zinc transporter 8

List of Publications

Akata, E., Mabhala, A., Cooper, H. & Bowen-Jones, D. (2016). A meta-analysis of type 1 diabetes mellitus, all-cause and causes-specific mortality. Retrieved from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016037564

A systematic review and meta-analysis of all-cause and cause-specific mortality and Type 1 diabetes including gender specific risk and time-based trends Volume34, IssueS1 Special Issue: Abstracts of the Diabetes UK Volume34, IssueS1Special Issue: Abstracts of the Diabetes UK Professional Conference 2017, Manchester Central, Manchester, 8–10 March 2017 Professional Conference 2017, Manchester Central, Manchester, 8–10 March 2017

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Chapter 1: Introduction and Literature review

1.1 Background

The World Health Organisation (WHO) defines diabetes mellitus as a group of chronic metabolic disorders of endocrine origin, characterised by chronic hyperglycaemia associated with alterations in the metabolism of carbohydrates, fats and proteins. This occurs as a resultant effect of defects in the action or production (relative or absolute deficiency) of insulin, a hormone that regulates glycaemic control (World Health Organisation [WHO], 1999; George, & Alberti, 2010; American Diabetes Association [ADA], 2014). Chronic hyperglycaemia is the main clinical feature of this condition and uncontrolled, predisposes an individual to acute and chronic complications. Diabetes has an estimated global prevalence of 8.8% and is expected to rise to 9.9% in 2045. It was estimated to affect 424.9 million people in 2017 with a projected rise to 628.6 million in 2045. The global healthcare expenditure on diabetes in 2017 had an estimate of USD 727 billion with the projected increase to USD 776 billion by 2045 (International Diabetes Federation [IDF], 2018).

According to a broad aetiological classification based on glycaemic disorders, diabetes mellitus falls into specific groups. These are; type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes (GDM) and other specific types (Kuzuya & Matsuda, 1997; World Health Organisation [WHO], 1999; George & Alberti, 2010; American Diabetes Association [ADA], 2014). T1D is further categorised based on aetiology into either being autoimmune or idiopathic in origin (American Diabetes Association [ADA], 2014).

Type 1 diabetes (T1D) had previous phenotypic classifications of 'Insulin-dependent diabetes' (IDDM) and juvenile onset diabetes (Kaul et al. 2013). T1D is a long-term condition requiring lifelong treatment with insulin therapy. Although it accounts for between 5 – 10 % of the total number of people who have diabetes, it still contributes significantly to the overall burden of diabetes as a whole.

The global prevalence of T1D is estimated to be over 1 million children and adolescents having the condition (International Diabetes Federation [IDF], 2017), with a yearly rate of increase in incidence ranging between 0.6 to 9.3% (Patterson et al. 2009). However, variations in incidence exist across regions, countries and ethnic backgrounds. The UK ranks fifth highest in incidence after Finland, Sweden, Saudi Arabia, and Norway. The incidence rate remains very high at 22.8 per 100,000, with an increase of 4% annually (Diabetes UK, 2014, 2017). Prevalence estimate of T1D in the UK is 187.7 per 100,000. In the UK, current estimates of those living with this

condition are almost 400, 000 individuals. More than 90 % of all children with diabetes suffer from T1D (Juvenile Diabetes Research Foundation [JDRF], 2017). Previous estimates of the prevalence of the condition reveal that in 2013, the rate of children and young people (CYP) with T1D was between 1 per 430 to 1 per 53,012. For children who were younger than the age of 14 years, incidence rates were estimated to be 24.5 per 100,000 with an increase to 25.9 per 100,000 in 2016 (Diabetes UK, 2013; 2017).

Variations in the global incidence as noted in table 1.1 using an arbitrary system of classification into very low, low, intermediate, high and very high to highlight this trend. Observation of this trend reveals higher incidence rates in temperate regions with a gradual decline towards the hotter climates. In Asia, the incidence rates are very low (<1/100,000 per year) except Kuwait which has an incidence rate of 22/100,000/year. Countries in the African continent have incidence rates of very low to intermediate incidence rates (<1/100,000 per year - 5-9.99/100,000 per year). Populations from South America, Central America and the West Indies have different incidence rates from low to High (1-4.99/100,000 per year - 10-19.9/100,000 per year). Many countries in Europe and North America were noted to have high to very high incidence rates (10-19.9/100,000 per year - ≥20/ 100,000 per year).

In the UK, the peak age of diagnosis is in the age group 10 – 14 years with an observed increasing trend (Diabetes UK, 2014; Diabetes UK, 2017). This is comparable to what is observed globally with noted variations across populations, age and sex groups (The DIAMOND project group, 2006; Diabetes UK, 2013; Llenasa et al. 2015). Some studies suggest average increases of 5.4%, 4.3%, 2.9% for the 0-4 year, 5-9 year and 10-14 year age groups respectively, reflecting the strongest increase in incidence rates noted among the younger age group < 5 years (Pattterson et al. 2009; The DIAMOND project group, 2006).

Table 1.1: Patterns in incidence rates of T1D across countries (adapted from IDF Diabetes Atlas 8th edition, 2017).

Patterns of incidence variation	**Countries/regions represented**
Very low incidence (<1/100,000 per year)	Venezuela, Peru, Pakistan,
Low incidence (1-4.99/100,000 per year)	Japan, Cuba, Chile
Intermediate incidence (5-9.99/100,000 per year)	Italy, France, Egypt
High incidence (10-19.9/100,000 per year)	USA, Australia, Germany, Spain, Italy.
Very high incidence (≥20/ 100,000 per year)	Finland, Sweden, UK, Kuwait, Saudi Arabia, China, Norway, Russia.

Estimating the real financial burden of T1D is difficult. However, a study by Hex et al. (2012) revealed a significant burden on the UK economy. This study estimated the direct cost and indirect cost of the burden of T1D to be £1bn and £0.9bn respectively with a projected rise to approximately £1.8bn and £2.4bn respectively in 2035/2036. Similar trends are also observed in other countries, for instance, a study by Tao et al. (2010), suggested the US spent approximately $14.4bn for T1D in direct medical cost and income lost. Another study in Spain, analysing the accrued expenses of 249 individuals with T1D, estimated the average direct healthcare cost to be €4070 per annum per individual and indirect (non-healthcare/informal) cost to be €23,204 per annum per individual (López-Bastida et al. 2017). The burden of T1D does not only accrue financially, but several other dimensions also contribute to its overall burden such as the health-related impact, social impact and economic impact (Murillo et al. 2017; Rydén et al. 2016; Jacobson et al. 2013; Graue et al. 2003; Wu et al. 1998). As such, this is evident on the effects on the health infrastructure as it pertains to health seeking, user satisfaction, quality of life and direct health cost implications. The health impact evolves from the diagnosis of T1D on morbidity and mortality, treatment and complication. The social impact relates to person hours lost due to illness episodes, impacts on family, caregivers and society at large. The economic impact relates to the direct and indirect cost of providing services, other associated financial implications, and indirect financial cost as it relates to loss of productivity (Rydén et al. 2016).

The diagnosis of T1D heralds the development microvascular and macrovascular complications. Microvascular complications result from the sustained effect of hyperglycaemia on blood vessels, nerves and various organs. The resultant effects are varying degrees of retinopathy and neuropathy that may manifest with sexual dysfunction and reduced peripheral sensations predisposing to ulcers. Nephropathy occurs in patients who may present with microalbuminuria, and progressive chronic renal impairment leading to renal failure (Daneman, 2006; Pietrzak et al. 2013). Macrovascular complications result from a cascade of biochemical abnormalities, with the principal contribution being hyperglycaemia that culminates in arteriosclerosis and its untoward effects. These complications constitute an elevated risk of cardiovascular conditions (myocardial infarction, ischaemic heart disease, and heart failure), cerebrovascular diseases (ischemic and haemorrhagic stroke), and hypertension. There is also increased risk of chronic infections of the skin, cognitive decline and autonomic impairment (diabetic foot). Other associated complications are a risk of psychiatric conditions, increased risk of morbidity and mortality, and reduced life expectancy. Pregnant women with

T1D have an increased risk of macrosomia and large for gestational age (LGA) babies. Other complications in pregnancy include polyhydramnios, pre-eclampsia, preterm delivery, early foetal loss, congenital malformations, perinatal and neonatal mortality (Evers, de Valk, & Visser, 2004; Jensen et al. 2004; Persson, Norman, & Hanson, 2009; Hod et al. 2008). The impact of these complications in T1D confers increased mortality risk as compared to the general population; research also suggests that mortality attributed to T1D and its complications vary according to regions, countries, sex and age groups (Soedamah-Muthu et al. 2006).

Mortality in T1D attributed to the acute complications occur within the younger age groups (<30 years), while cardiovascular complications account for most of the deaths from chronic complications (Lind et al. 2015; Morgan et al. 2015; Huxley et al. 2015; Katz & Laffel, 2015; Snell-Bergeon, & Maahs, 2015; Tu et al. 2008). Research also links T1D to excess premature mortality which impacts gravely on survival and life expectancy (Livingstone et al. 2015; Katz & Laffel, 2015).

Cardiovascular disease (CVD) complications are found to be the most common macrovascular complication in T1D especially above the age of 40 years. Below 40 years, the most common complications are from acute complications including Diabetic ketoacidosis and severe hypoglycaemia (Liang et al. 2009; Huxley et al. 2015). CVD accounts for a ten-fold increase in the risk of a cardiovascular event (Orchard et al. 2006). Livingstone et al. (2012), in their study considering CVD risk and all-cause mortality in T1D, found an increased risk as compared to the general population. In the UK, CVD accounts for 44% of deaths in T1D, while diabetic nephropathy (DN) contributes to 21% mortality from ESRD. Mortality from T1D is burdened disproportionately to females as they have a 40% increase in the risk of all-cause mortality as compared to males (Huxley et al. 2015). A systematic review and meta-analysis on mortality in T1D is discussed further in chapter three.

Diabetic retinopathy (DR) is the most common ocular complication for T1D. It accounts for reduced vision and sometimes blindness among T1D patients between the ages of 20 and 79 years. A study by Esteves et al. (2009) found the prevalence of DR to be 44.4% in their study cohort. Another study highlighted the prevalence of DR to be 74.9% in blacks and 82.3% in whites' population subset (Roy et al. 2004). A study in the UK using a national registry found the prevalence of DR to be 56% in the cohort studied (Thomas et al. 2015). DR that becomes a threat to vision rarely occurs within the first 3 – 5 years following diagnosis or before puberty.

Consequently, nearly all patients with T1D have some form of DR after 20 years post-diagnosis inferring that duration of diabetes remains a powerful predictor of diabetic retinopathy (Fong et al. 2004). However, a recent study suggests that other strong predictors of DR include higher levels of glycated haemoglobin (HbA_{1c}) and low-density lipoproteins (LDL) levels (Romero-Aroca et al. 2017).

There remain considerable variations in the prevalence of diabetic neuropathy in T1D; they vary between 23 and 51% (Pop-Busui et al. 2009; Boulton et al. 2005; Young et al. 1993). The diagnosis of neuropathy is made difficult because of varying signs and symptoms which can be sensory, autonomic and/or motor. Neuropathy is a significant risk factor for the onset of foot ulcerations and the development of Charcot neuroarthropathy; it also increases the risk of non-traumatic amputations of the lower extremities (Abbott et al. 2002; Alleman et al. 2015). Neuropathy also increases the risk of disability with a poor quality of life (Vileikyte et al., 2005). The study by Abbott et al. (2011) found a weak correlation between increasing age and the painful symptoms of neuropathy; females were more likely to experience painful neuropathic symptoms than males. Ethnic variations were also highlighted in this study; the study found that the prevalence of clinical neuropathy was less in South Asians (14%) than Europeans (22%) and Afro-Caribbean (21%).

Diabetic nephropathy (DN), a complication of T1D, is recognised as albuminuria. It is recognised as the presence of increased urinary albumin excretion (UAE) without any other precipitating renal disease (Gross et al. 2005). Diabetic nephropathy can occur in stages: microalbuminuria (UAE >20 μg/min and ≤199 μg/min) and macroalbuminuria (UAE ≥200 μg/min). The onset of albuminuria is noted to occur at the rate of 2 - 3 % annually (Bjornstad, Cherney, & Maahs, 2014). The natural evolution of this complication is its progression to end-stage renal disease (ESRD). Despite therapeutic strategies in the control of DN, it remains one risk factor that contributes to the onset of coronary artery disease (CAD) and all-cause mortality. In 2009, it was responsible for 44.5% of mortality related to end-stage renal disease (ESRD) in the USA (Collins et al. 2010).

Glycaemic control remains one of the main predictors of cardiovascular disease complications and all-cause mortality (Sakurai et al. 2013; Zhao et al. 2014). The DCC/EDIC trial established that intensive glycaemic control was necessary to militate against the onset and progression of complications. The DCC/EDIC study established rates of retinopathy with a cumulative incidence of 50%, nephropathy rates where 25% and cardiovascular disease (CVD) rates were

14% in the conventional therapy population. Those in the intensive therapy arm experienced lesser rates of complications with incidence rates for retinopathy, nephropathy and CVD to be 27%, 9%, and 9% respectively (Lachin et al. 2014; Lachin et al. 2016). Those in the intensive therapy group were managed using insulin pumps or a minimum of three daily insulin injections for a mean duration of 6.5 years during which they maintained a mean HbA1c of approximately 7%. Those in the conventional arm also received treatment for an average of 6.5 years, they were managed with one or two doses of insulin, daily self-monitoring, received education on diet and exercises with minimal adjustments to daily insulin dosages with a target mean HbA_{1c} of approximately 9%. Several other studies also support the concept of early commencement of intensive therapy a term referred to as 'Metabolic Memory'. They argue that the early commencement of intensive therapy mitigates the long-term onset and progression of CVD complications (Agrawal et al. 2018; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group, 2016; Holman et al. 2016). An observational study with T2D population observed a U-shaped correlation with HbA1c and all-cause mortality, inferring increased mortality at the two polar ends of HbA1c levels (Currie et al., 2010). A similar finding was observed with T1D population subset in which the non-linearity of the relationship was highlighted between HbA1c levels and all-cause mortality. The study also found a U-shaped relationship between HbA1c levels and all-cause mortality, with increased mortality at HbA1c levels below 5.6% and above 11.8% (Schoenaker et al. 2014).

The increased risk of mortality starts at the time of diagnosis and subsequently accumulates throughout life. Following the diagnosis of T1D, the individual endures lifelong exposure to increased morbidity and increased risk of mortality; these have an adverse effect on the quality of life. Considerably, life expectancy in T1D remains lower than those without the condition. An overall estimation of reduction in life expectancy varies between 7 – 15 years. In a study by Livingstone et al. (2015), they found the expected life expectancy of males and females diagnosed with T1D at the age of 20 years was 66.2 years and 68.1 years respectively as compared to 77.3 years and 81 years for males and females without T1D. This indicated a reduced life expectancy of 11.1 years in males and 12.9 years in females.

Specific predicting factors influence survival and mortality patterns in T1D. There is limited evidence on the predicting factors on mortality in T1D. While a few studies focus on all-cause mortality in T1D, most of the studies focus on the risk of Coronary artery disease (CAD) which

is a significant contributor to mortality in T1D. A study by Soedamah-Muthu et al. (2014) highlighted age and albumin/creatinine to be the strongest predicting factors for all-cause mortality in T1D. Another study by Soedamah-Muthu et al. (2008) identified the risk factors of age, waist-to-hip ratio (WHR), pulse pressure, and non-HDL cholesterol as significant risk factors for increased mortality in T1D. The study by Olson et al. (2002) identified smoking, overt nephropathy, non-HDL cholesterol, HbA_{1c} and duration of diabetes as predictors of mortality. A study by Weis et al. (2001) suggests that some clinical and biochemical parameters were responsible for the onset of coronary artery disease and ultimately mortality. The parameters attributed to higher mortality rates were albuminuria (nephropathy), retinopathy, and lower apolipoprotein A1 levels. Participants who were more predisposed to the development of coronary artery disease were those with longer duration of diabetes, increasing age of onset of T1D, retinopathy and neuropathy. The study by Cusick et al. (2005) additionally identified amputation as a strong predictor of mortality. In the development of cardiovascular conditions, Stettle et al. (2007) found QT interval corrected for heart rate (QTc) was a strong predictor of long-term excess all-cause mortality owing to the increased risk of arrhythmia and death. Another study by Rewer et al. (2002) identified that in younger populations with T1D were at increased risk of mortality from DKA and hypoglycaemia, predictors of increased risk of severe hypoglycaemia were lower levels of HbA1c, increased duration of diabetes, and the presence of psychiatric disorders. Diabetic ketoacidosis (DKA) is a condition that results from persistent insulin deficit and subsequent rise in glucagon, epinephrine (adrenaline), norepinephrine (noradrenaline), cortisol, and growth hormone. These encourage the process of glycogenolysis, gluconeogenesis, ketogenesis, and other catabolic processes. For increased risk of DKA, the study highlighted predictors as higher levels of HbA1c, higher doses of insulin doses, and the presence of psychiatric disorders. In patients on intensive insulin therapy, predictors of mortality included the onset of nephropathy, duration of diabetes, smoking status, systolic blood pressure, cholesterol level, hypertension, the presence of retinopathy and socioeconomic status (Mühlhauser et al., 2000). While some of these risk factors are modifiable, others are not.

To understand all-cause mortality and cause-specific mortality among T1D patients, it is essential to get a better understanding of the predicting risk factors that influence survival and mortality in T1D. This would help to inform clinical practice in the management of T1D patients.

1.2 Clinical presentations of T1D

T1D presents with a myriad of symptoms. The classic presentation of symptoms in children and young adults (CYP) are; hyperglycaemia (random plasma glucose more than 11 mmol/litre), polyuria, polydipsia, polyphagia, weight loss and excessive tiredness (Roche, Menon, Gill, & Hoey, 2005). However, for some individuals, especially the very young (between 2-5 years), their initial presentation may be acute onset diabetic ketoacidosis (DKA). Almost a third of all patients have an acute presentation of DKA (Neu et al. 2003; Roche et al. 2005).

Polyuria (increase in the amount and frequency of urination) is often as a result of hyperglycaemia which causes osmotic diuresis. In some instances, polyuria also presents as nocturnal enuresis (increase excretion of urine at night). Another untoward effect of hyperglycaemia is the onset of dehydration, hypovolaemia and hyperosmolar state as such the affected individual remains in a state of excessive thirst. Insulin deficiency promotes a catabolic state that encourages the breakdown of muscles proteins, lipogenesis, and electrolyte imbalance.

Persistent hyperglycaemia also influences the ability of the body to fight infections as the protective ability of phagocytes becomes impaired. Therefore, it is common for T1D patients to present with skin and muco-membranous conditions like Staphylococcal pustules, abscesses, carbuncles, vaginal candidiasis, balanitis, and in rare situations, necrotising fasciitis, Fournier gangrene, and mucormycosis of the maxillary sinus (Yanar et al. 2006, Dworkin et al. 2009).

DKA usually presents with a triad of hyperglycaemia, acidosis and ketonuria (Pietrzak et al. 2013). It reported incidence ranges from 0-56 per 1000 person-years while its prevalence is between 0-128 per 1000 persons (Fazeli Farsani et al. 2017; Rewers et al. 2015). The condition may present clinically with the classic signs of hyperglycaemia as well as complaints of malaise, muscle cramps, and gastrointestinal symptoms, which may mimic acute abdomen. Gastrointestinal symptoms include; nausea, vomiting, abdominal discomfort, acute fatty liver, right upper quadrant pain, and visceral autonomic neuropathy (Fazeli Farsani et al. 2017). Some clinical signs encountered in diagnosing this condition are dehydration, Kussmaul respiration (deep sighing respiration), ketone breath (sweet smell fetor), and altered consciousness, which can lead to death if untreated.

T1D is associated with an increased risk of cardiovascular diseases (CVD) (de Ferranti et al. 2014; Albers et al. 2010). Macrovascular presentations of T1D are acute myocardial infarction

(AMI) and acute stroke. Patients present with symptoms of acute chest pain, but sometimes with atypical chest pain. Patients with T1D also have an elevated risk of stroke with symptoms such as facial weakness, slurred speech and weakness of the limbs (Ståhl et al. 2017; Sundquist, & Li, 2006).

Patients may also present with microvascular complications such as acute loss of vision from diabetic retinopathy. Some studies highlight that almost half of the patients (44.4%) with T1D may present with symptoms of diabetic retinopathy (Esteves et al. 2009). The sustained hyperglycaemic state encourages the osmotic engorgement of the eye lenses, altering its focal elasticity and resulting in blurred vision.

Some patients with T1D may present with symptoms of neuropathic syndromes from peripheral neuropathy, mononeuropathy to amyotrophy (Sima, & Kamiya, 2006; Sima, Zhang, & Grunberger, 2004). Peripheral neuropathy presents in multiple ways relating to site; it may manifest as sensory, focal/multifocal, and autonomic neuropathies (Fowler, 2008). The presence of peripheral neuropathy in addition to complications of the peripheral vascular disease (PVD) may result in the onset of diabetic foot ulcers. These conditions expose the patient to an increased risk of amputation (Jain, 2016; McInnes, 2012; Clayton, & Elasy, 2009).

Many individuals with T1D experience numerous episodes of hypoglycaemia that go undocumented but the mean incidence of symptomatic hypoglycaemia is around two episodes per week. However, documented evidence reveals that severe debilitating hypoglycaemia requiring intervention has a prevalence of between 30 and 40 per cent per year, and an annual incidence of 1.0-1.7 episodes per patient per year (McCrimmon, & Sherwin, 2010; Frier, 2009).

1.3 Diagnosis of T1D

The diagnosis of T1D presents a complex and challenging situation to the patient, families and caregivers and as such has a long-term impact on families and healthcare teams (Simms, & Monaghan, 2016; Jönsson, Lundqvist, Tiberg, & Hallström, 2015; Helgeson, Becker, Escobar, & Siminerio, 2012). Primary care is the first point of contact and usually the setting for diagnosis of most cases. However, some cases present to secondary care in the form of acute complications such as DKA and severe hypoglycaemia where the diagnosis is made. In the UK, NICE guidelines (NG17, NG18, and NG19), provide the basis for diagnosis and management.

1.3.1 Glycemic diagnostic criteria

The diagnosis of T1D is obtained by the clinical presentation of diabetes and laboratory findings of hyperglycaemia as defined by the WHO (2017) and ADA (2011). The glycaemic criteria for glucose abnormalities are illustrated in Table 1.2

Table 1.2 Diagnostic criteria for glycaemic abnormalities (adapted from WHO, 2011; ADA, 2010).

Diagnosis	**FPG≥8hours**	**2 hours post glucose load (75g oral glucose)**	**Random test**	**HbA_{1c}(mmol/mol[%])**
Normal	<5.5mmol/l (<100mg/dl)	<7.8mmol/l (<140mg/dl)	-	20-40 [4.0-5.9%]
Impaired fasting glucose (IFG)	6.1-6.9mmol/l 100-125mg/dl	<7.8mmol/l	-	42-46 [6.0-6.4%]
Impaired glucose tolerance (IGT)	<7.0mmol/l 126mg/dl	≥7.8mmol/l but <11.1mmol/l	-	40-46 [6.0-6.4%]
Diabetes Mellitus	≥7.0mmol/l ≥126mg/dl	≥11.1mmol/l ≥200mg/dl	≥11.1mmol/l ≥200mg/dl and clinical symptoms	≥48 ≥6.5%

NB:

Fasting plasma glucose (FPG): This test is done after an overnight fast of a minimum of 8 hours, a venous sample of blood is collected for laboratory estimation of blood glucose.

Random plasma glucose (RPG): This is the estimation of venous plasma glucose from an individual not fasted with no regard to the time of last meal.

Table 1.3: Diagnostic criteria for Diabetes (adapted from WHO, 2011; ADA, 2010).

A) T1D symptoms (e.g. polyuria, polydipsia and unexplained weight loss for Type 1) plus:

- A random venous plasma glucose concentration ≥ 11.1 mmol/l or
- A fasting plasma glucose concentration of ≥ 7.0 mmol/l (whole blood ≥ 6.1 mmol/l) or
- Two-hour plasma glucose concentration ≥ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT).

If at the time of diagnosis, there are no apparent clinical symptoms, the diagnosis should be confirmed with at least one additional glucose test result on another day of which a value in the diabetes range is essential, either fasting, from a random sample or the two-hour post glucose load. If the random fasting values are not diagnostic, then the two-hour value should be used.

1.3.2 HbA_{1c} estimation

In 2010, an international expert committee comprising members appointed by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), the International Diabetes Federation (IDF) and the WHO proposed the use of HbA1c estimation in the diagnosis and prognostication of diabetes (WHO, 2011; ADA, 2010; Kilpatrick, Bloomgarden, & Zimmet, 2009). Glycated haemoglobin (HbA_{1c}) is formed from a ketoamine reaction involving the irreversible glycosylation of the N-terminal valine residue of one or two beta globin chains. It is an estimate of the beta-N-1-deoxy fructosyl component of haemoglobin. The turnover rate is dependent on the lifespan of red blood cells (RBC) and correlates closely to a period of between 90-120 days (Gupta, Jain, Chauhan, 2017). This gives a diagnostic advantage of its use in diagnosis and prognosis in diabetes. Its fraction remains elevated in a state of persistent hyperglycaemia and its weighted average remains constant in fasting and non-fasting states (Leow, 2016; Bry, Chen, & Sack, 2001). Table 1.4 illustrates its use in the diagnosis of T1D.

Table 1.4: HbA_{1c} use in diagnosis (adapted from diabetes.co.uk)

HbA1c	**mmol/mol**	**%**
Normal	Below 42 mmol/mol	Below 6.0%
Prediabetes	42 to 47 mmol/mol	6.0% to 6.4%
Diabetes	48 mmol/mol or over	6.5% or over

1.3.3 Value of testing for pancreatic autoantibodies and genetic testing

Before the clinical onset of T1D, autoantibodies produced to pancreatic islets cells indicate the prodromal phase. These autoantibodies can be assayed for diagnosis and prognosis of disease progression. Five pancreatic autoantibodies identified as necessary in the disease process of T1D are Islet Cell Cytoplasmic Autoantibodies (ICA), Glutamic Acid Decarboxylase Autoantibodies (GADA), Insulinoma-Associated-2 Autoantibodies (IA-2A), Insulin Autoantibodies (IAA) and zinc transporter 8 (ZnT8). The presence of three to four of these autoantibodies is highly suggestive of diagnosis or progression of T1D (Calderon, & Sacks, 2014; Sacks et al. 2011). Their presence can be used to determine the autoimmune form of T1D and also differentiate T1D for T2D and MODY (Zeigler et al. 2013). However, critics for their use in diagnosis argue that there is no routine comprehensive use of these tests clinically, and they possess lower rates of positivity if measured long after diagnosis or in adulthood (Bingley, 2010; Bingley et al. 1997). Table 1.5 below summarises the use of autoantibodies in the diagnosis of T1D.

Table 1.5: Autoantibodies used in the diagnosis of T1D

Test	**Description**
Islet Cell Cytoplasmic Autoantibodies (ICA)	Autoantibody that usually is detected at the onset of T1D. Detection rates of 70-80% at the time of diagnosis.
1.1 Glutamic Acid Decarboxylase Autoantibodies (GADA)	Autoantibody that is usually detected at the onset of T1D. Detection rates of 70-80% at the time of diagnosis.
Insulinoma-Associated-2 Autoantibodies (IA-2A)	Detection rates of almost 60% in T1D.
Insulin Autoantibodies (IAA)	Detected rates of almost 50% of T1D children; not commonly detected in adults
Zinc transporter 8 (ZnT8)	Detection rates of almost 30% in T1D with undetectable levels of other predictor autoantibodies (GAD65Ab, IA - 2Ab and IAA)

Although genetic screening is not routinely used in clinical practice, recent evidence suggests the clinical relevance of the use of Genetic risk scores (GRS) or polygenic score (Cooke Bailey, & Igo, 2016). It is a tool that can examine the cumulative risk of the genetic and intermediate traits or risk factors in the prediction of a disease condition. Factors to consider when creating GRS are contributions from genetic variations, weighting and comparability across ethnic groups. GRS are usually generated using genome-wide meta-analyses to accumulate information on a particular disease condition (Morrison et al. 2007). GRS has potential use of risk prediction in high-risk populations, gene-by-environment interaction studies, and

Mendelian randomisation studies (Cooke Bailey, & Igo, 2016). Its use is also relevant in a situation when there is diagnostic difficulty in accurately classifying patients with diabetes because of equivocal evidence from autoimmune markers and clinical features. Oram et al., (2016) used the GRS to precisely differentiate between the types of diabetes, and also made accurate predictions of those (adults) who in early diagnosis would require insulin treatment with disease progression.

1.4 Management of T1D

The management of T1D in the UK is governed by NICE guidelines (NG17, NG18, and NG19). The core of these guidelines is the delivery of services using a patient-centred approach. These guidelines are regularly updated every 2-4 years and are generated following extensive consultation with various stakeholders (NICE, 2017). These guidelines are set up with the overarching aims of reducing the burden of T1D by providing the necessary tools, services and information to adequately attain near to normal glycaemic levels, reducing and slowing down the onset and progression of complications, and reducing morbidity and mortality from this condition (NICE, 2015a). The NICE guidelines propose several management algorithms and clinical knowledge summaries (CKS) that provide advice on various aspects of management in T1D, these are but not restricted to the following;

- Monitoring of blood glucose levels
- Appropriate treatment modalities for glycaemic control
- Monitoring of albuminuria, lipid profiles and blood pressure
- Appropriate treatment guidelines to identify the onset and limit the progression of complications in T1D
- Appropriate advice on patient centred management and care, including educational, lifestyle and dietary management
- Identification of cardiovascular risk and interventions to control cardiovascular risk
- Advice on inpatient care

Routine care usually takes place in secondary care settings and backed up by primary care, hence the need for incorporation of a multidisciplinary team in patient care and optimisation of cost-effectiveness.

For children and young people (CYP), and adults, the initial approach to management once the diagnosis is made is the provision of an integrated care package by a multidisciplinary team.

They undertake and provide detailed initial assessment, ongoing agreed plan of care and follow up, and details of the annual review process.

Assessments include medical, environmental, cultural and educational assessments (NICE, 2016b). The medical assessment considers the detailed history of the condition, evaluation vascular risk factors such as smoking status, Blood pressure, BMI, foot, and eye examination, biochemical parameters such as albumin:creatinine ratio, HbA_{1c} levels, TSH. Other areas considered during the medical assessment include the psychological well-being of the patient, the patient's attitude toward self-care and medication (NICE, 2016b). Environmental assessment involves ascertaining the impacts of home, social and work environments on the condition of the patient and influence of support structures such as family and friends. Also considered is the impact of lifestyle factors such as alcohol, smoking and substance abuse. The cultural and educational assessment considers the prior knowledge of the individual to enable measures to be designed to ensure appropriate treatment modalities, and incorporation into educational programmes (NICE, 2016b).

Providing an integrated care package helps to optimise the level of care thereby reducing the risk of development or progression of complications. Home-based or inpatient care can be offered depending on the preference and clinical needs of the patient (NICE, 2015c). It is essential that at this time initial contact details and the roles and responsibility of members of the diabetes care team are identified and explained to the patient and caregivers. A person should be identified as the primary contact whose responsibility is to provide information about access to services, especially at crucial points in management such as initial stage of diagnosis, change in treatment approach, referral to other services within the diabetes care team and transition services from paediatric to adult clinics. This role is sometimes best performed by the diabetes specialist nurse (DSN). Other possible functions of the DSN are to provide supportive services or direction in tackling problems, providing information on lifestyle, and telephone follow up appointments. Other members of the team, like the dietitians, provide dietary advice in line with treatment goals. Clinical psychologists can provide ongoing psychological support, and identify potential barriers to the uptake of treatment. If required, it is pertinent that an efficient system of communication is developed to ensure adequate communication between members of the diabetes team across disciplines and between primary, secondary, and community settings (Diabetes UK, 2005, 2009). Patients are encouraged to participate in continued education programmes that meet their individual needs. These programmes consider specific issues such as emotional well-being, age and maturity of the

patient, influence from culture, current diabetes knowledge, social circumstances, and life goals (NICE, 2015a). The educational programmes are designed to convey information on details of insulin therapy which encompasses its use, mode of delivery, its aims and dosage regulation. Approach to blood glucose control is taught with an emphasis on adequate self-monitoring of blood glucose or HbA_{1c} levels according to agreed management targets (NICE, 2016a). Following an adequate understanding of the use of understanding of insulin use and blood glucose measurements, the focus is further understanding of the effects of diet, physical activity and intercurrent illness on glucose control (NICE, 2016a). Emphasis on what measures to take during intercurrent illness episodes are taught like the need to understand 'sick-day' rules, with measurement for ketones. They are also taught to understand the signs and symptoms of hypoglycaemia, hyperglycaemia and ketosis and measures to take during those periods (NICE, 2016a).

1.4.1 Blood glucose control

NICE advocates that the treatment target is set considering individual capabilities and preferences. Other factors needed to determine treatment targets are activity levels, the presence of comorbidities, complications and the risk of developing hypoglycaemia. These targets should target close to normal glycaemic levels as possible. The NICE guidelines in 2015, stipulate HbA_{1c} targets should be levels of ≤ 48mmol/mol (6.5%). Prior to 2015, target levels for HbA_{1c} were set at ≤ 58 mmol/mol (7.5%) for CYP (NICE, 2015a, 2015b). However, there was a need to further reduce to current levels to conform to levels obtainable in adult services, which ensured uniformity between adult and paediatric services, hence a smoother transition from children to adult services. This also had the added advantage of reducing the risk of long-term complications. Optimum levels of assessment for HbA_{1c} are set at four times a year, but higher for sub-optimum glycaemic control (NICE, 2015a, 2015b).

Routinely, to ensure optimum glycaemic control, it is essential that regular self-monitoring of glucose levels be done. CYP including their family and carers are recommended to ensure a minimum of five checks per day for glycaemic levels. In adults, it is recommended that a minimum of four checks per day be done for glycaemic levels. They should aim for;

- Fasting plasma glucose level of 4–7 mmol/litre on waking.
- A plasma glucose level of 4–7 mmol/L before meals (pre-prandial).
- A plasma glucose level of 5–9 mmol/L at least 90 minutes after meals (post-prandial).
- A plasma glucose level of at least 5 mmol/L while driving, if they are of driving age.

Several methods of glucose monitoring exist, and preference is made depending on clinical factors and individual preferences. These include self-monitoring using glucose meters and finger pricks. The subcutaneous flash glucose monitoring system, for example, the FreeStyle Libre Flash glucose monitoring system measures interstitial fluid glucose using a meter and a sensor placed subcutaneously. This eliminated the need for regular finger-prick measurements and performed at similar levels to continuous glucose monitoring (CGMs) systems (NICE, 2015a, 2015b).

Subcutaneous flash glucose monitoring systems do not have high or low alarms and are not as ideal in those with recurrent severe hypoglycaemia or hypoglycaemia unawareness. These CGMs adopts a system that employs the use of subcutaneous sensors which measure glucose levels every 1-5 minutes; they can be set up with integrated alarm systems which intimate the user of high and low glucose levels including rapidly rising and falling glycaemic levels. Flash glucose monitoring systems and CGMs have the main advantage of being less invasive, eliminating the need for multiple needle pricks during the day. Additionally, CGM intimate alarms of high and low glucose levels that are of great value at night time (Diabetes UK, 2015).

1.4.2 Insulin use and hypoglycaemia

Treatment in T1D involves the lifelong use of insulin. Insulin therapy should only be started and overseen by healthcare professionals with the requisite capability and training. Several factors are considered with the administration of insulin, including the age of the individual, dexterity of handling cartridges, the presence of visual impairment, needle phobia, HbA_{1c} targets and patients' preferences (NICE, 2016a). Insulin therapy aims to closely mimic the physiological mechanisms of insulin function in the human body. There are three types of insulin offered as treatment options in the UK; these are human insulins, human insulin analogues, and animal insulins (which are now rarely used). Insulins are classified mainly based on their profile of time action. Short-acting insulin closely resembles the immediate physiologic release of insulin to a glucose meal, intermediate and long-acting insulins emulate continuous basal release of daily insulin.

In practice, individuals with T1D undertake self-monitoring of blood glucose levels and adjustment of insulin doses based on glycaemic levels. Insulin replacement involves the use of basal insulin and pre-prandial (pre-meal) insulin. The basal insulin preparations are either long-acting (glargine or detemir) or intermediate-acting (NPH). Pre-prandial insulin preparations are rapid acting (lispro, aspart, insulin inhaled, or glulisine) or short-acting (regular).

Insulins are classified based on their formulations or action profiles — classification based on human or animal insulin. The production of human insulin undergoes the manufacturing process that utilises recombinant DNA technology to produce similar variants having the same amino acid sequence as endogenous human insulin. Inputs can be made to alter and produce specific properties such as prolonged duration of action or faster absorption and action. Animal insulins are insulin preparations extracted from animal sources such as cows (bovine insulin) or pigs (porcine insulin).

Regarding action profiles, insulin is classified into short-acting, intermediate-acting (Isophane or NPH [Neutral Protamine Hagedorn]), and Long-acting insulins (Dawoud et al. 2017; Muis et al. 2006; Hirch, 1999). Short-acting insulins are characterised by fast action of onset and short duration of action. Commonly, two types exist, soluble insulins which have an onset action time of 30-60 minutes and can remain active for approximately 8 hours (Human Actrapid® and Humulin S®). Also available are the rapid-acting insulin analogues with a more rapid onset of action (≤ 15 minutes) and approximate duration of action of 2 – 5 hours, they include Humalog® (insulin lispro) and Novorapid® (insulin aspart). Intermediate-acting insulins, examples of which include Humulin I®, Insuman basal®, and Human Insulatard®, act by emulating the effects of basal insulin with the onset time of approximately 2 hours, peak action of 4 – 12 hours and 16 – 35 hours in duration of action (Dawoud et al. 2017). Long-acting insulins have longer durations of action than intermediate insulin, and attain optimum levels beyond 24 hours, hence providing steady-state insulin levels, examples are Lantus® (insulin glargine), Levemir® (insulin detemir), and Tresiba® (insulin degludec).

Hypoglycaemia is the main side effect of insulin use; it is reported to have an incidence of almost 16% in T1D. However, this value is said to be underreported, as so many episodes of hypoglycaemia (≤ 3.9mmol/L [≤ 70mg/dl] are asymptomatic and go unreported. Symptomatic hypoglycaemia has an incidence of two (2) episodes per week in T1D, and severe hypoglycaemia requiring intervention has an incidence of 1.0 – 1.7 episodes per patient per year and yearly prevalence of 30 – 40% (McCrimmon, & Sherwin, 2010; Shafiee et al. 2012; Cryer, 2015). Recurrent episodes of severe hypoglycaemia subsequently blunt the body's counter-regulatory mechanisms leading to autonomic dysfunction. This further result in reduced hypoglycemic awareness and the consequent hypoglycaemic-associated autonomic failure sometimes leading to unexpected death or "dead-in-bed" syndrome. "Dead-in-bed" is likely to account for approximately 5% mortality in T1D. A possible explanation of this phenomenon is nocturnal hypoglycaemia inducing cardiac dysrhythmia and elongation of QTc

with underlying subtle cardiac neuropathy and electrolyte abnormality (Weston, 2012). Predictors of severe hypoglycaemia include previous hypoglycemic episodes, long-term use of insulin. Other side effects from the use of insulin include dermatologic reactions like lipodystrophy, transient bilateral presbyopia, weight gain, transient gastrointestinal upset, possible atherogenic effects on the cardiovascular system and rarely immune and hypersensitivity reactions (Lebovitz, 2011; Reichard, Nilsson, & Rosenqvist, 1993).

1.4.3 Use of Statins and Angiotensin-converting-enzyme inhibitor (ACE inhibitor) to the limit the progression of complications in T1D

T1D conferred significantly increased risk of mortality from acute complications of diabetic ketoacidosis, or exhaustion from deficient nutrient state secondary to the inherent catabolic state. With the advent of insulin therapy, individuals with this condition were afforded the opportunity to live longer; as such, they were prone to the onset of long-term complications of T1D. These are microvascular complications affecting several organs (eyes, kidneys, heart, blood vessels, and nerves) resulting in retinopathy, nephropathy, and neuropathy. These further exacerbate macrovascular complications (cardiovascular disease, cerebrovascular disease, stroke), which are primarily a result of atherosclerotic changes in blood vessels. Several large scale studies have been conducted to shed more insight into the management of T1D, including the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC), UK Prospective Diabetes Study (UKPDS), Framingham Heart Study (FHS), Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial, and the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial [AdDIT] (Gubitosi-Klug, et al. 2014; Marcovecchio et al. 2017; Zoungas et al.2017; Mahmood et al. 2014; Rubins, Robins, & Collins, 1996).

The DCC/EDIC trial advocated the central theme of tight glycaemic control to mitigate the onset and progression of T1D complications (neuropathy, nephropathy, and retinopathy). It also had the potential impact of reducing cognitive decline and improvement in health economics for healthcare systems (Martin et al. 2014; Aiello et al. 2014; Gubitosi-Klug et al. 2014). The intensive treatment program of tight glycaemic control in the DCCT showed beneficial effects on limiting the onset and progression of atherosclerosis and cardiovascular diseases, hence mitigating the incidence of macrovascular complications such as myocardial infarctions [MI], coronary artery disease [CHD], and stroke (Lachin et al. 2014). It also demonstrated a reduction of microvascular complications (retinopathy, neuropathy and

nephropathy) by 35% as compared to 90% on those on conservative therapy (Nathan et al. 2014; Kim et al. 2014).

NICE guidelines advise on the management of cardiovascular risk factors such as adequate management of blood pressure and lipid profiles with the introduction of lifestyle changes and/or the use of medications. Studies show that there is an increased risk of cardiovascular diseases with T1D which are inclusive of coronary heart disease (CHD), heart failure, cardiomyopathy, cerebrovascular disease, and peripheral artery disease (PAD). Some studies indicate an increased relative risk of almost ten times that of the general population (Libby et al. 2005; de Ferranti et al. 2014). This is due to the association between elevated blood pressure and the development of coronary artery disease (CHD) and stroke (Rosendorff et al. 2015). Studies have established hypertension as a significant independent risk associated with CHD regardless of age, race, or sex. There is a two-fold increase in the risk of having a coronary event with every 20mmHg increase in systolic blood pressure (SBP) or 10mmHg increase in diastolic blood pressure (DBP). In middle age, a reduction of SBP by 10mmHg (5mmHg DBP) confers a 50-60% reduction in the risk of developing stroke and a 40-50% reduction in the risk of developing CHD (Lewington et al. 2002; Lackland et al. 2014, Rosendorff et al. 2016). NICE suggest that the ideal target blood pressure readings for those with T1D should be levels of $\leq$ 135/85mmHg. The threshold for the introduction of blood pressure management is the BP $\geq$ 140/90mmHg for T1D patients with a target of $\leq$ 135/85mmHg in those without end organ damage and < 130/80mmHg in those with end organ damage (NICE, 2004, 2009, 2015).

Several documented trials advocate the effects of angiotensin-converting enzyme inhibitors (ACE-I) as anti-hypertensive linked to reduction in cardiovascular disease (CVD) outcomes, and also the advantage of the reduction in onset and progression of albuminuria in T1D. This is achieved through the maintenance of the glomerular filtration rate by preserving the renal ultrastructure (Yusuf et al. 2000; Fox, 2003; Julius et al. 2006). The use of statins has also been found to provide beneficial effects by reducing levels of harmful lipids, hence providing cardio-protection. A study by the Cholesterol Treatment Trialists' (CTT) Collaborators showed a risk reduction of 25% in cardiovascular disease events for every 1.0mmol/l fall in low-density lipoprotein cholesterol (Shah, 2014; Minder, Blumenthal, & Blaha, 2013; Cholesterol Treatment Trialists' (CTT) Collaborators, 2012). Until recently, there remained the question of using ACE-I and statins in adolescent T1D patients, pregnant women, and women of child bearing age. However, a recent study by Marcovecchio et al. (2017) revealed that the introduction of ACE-I and/or statin therapy did not have any significant impact on albumin:

creatinine ratio. While the use of ACE-I was found to reduce the incidence of microalbuminuria, Statins use led to reductions in total, low-density lipoprotein, and non–high-density lipoprotein cholesterol levels, and triglyceride levels.

1.5 Screening for thyroid and coeliac conditions in T1D

Coeliac disease and T1D share common genetic connotations. The prevalence of CD and T1D is between 1.6 -16.4%. There is a negative correlation between the age of onset of T1D and the risk of developing CD. Depending on the mode of onset for CD which can either be before the diagnosis of T1D (10-25%) or after the diagnosis of T1D (70-80%), it negatively influences the prognosis of T1D by predisposing the patient to further complications such as osteopenia. Autoimmune thyroid diseases (AITD) are also prevalent in T1D especially in those with multiple co-morbidities of T1D and coeliac disease (CD). Although there is limited evidence of the direct link between T1D and AITD, research suggests a disproportionate genetic link between CD, T1D and AITD. Also, the other clinical effects of CD and AITD may negatively impact on complications, morbidity and quality of life hence the need for screening at the time of diagnosis of T1D and between 2 to 5 years after diagnosis in children (Kurien et al. 2016; Bakker et al. 2016; Pham-Short et al. 2015; Cohn, Sofia, & Kupfer, 2014; Gabriel et al. 2011; Djuric et al. 2010; Cerruti et al. 2004).

1.6 Patient education and lifestyle modification

The cornerstone to the delivery of diabetes services is patient empowerment. Patient empowerment is defined as the process of nurturing an individual with appropriate knowledge to enable them to develop the necessary skills, attitudes and beliefs, which influence behavioural changes tailored to enhance the quality of life (Funnell et al., 1991; Allgot, 2001). One method of facilitating patient empowerment is through patient education where the process aims to equip individuals with abilities and opportunities to preserve their autonomy. Education promotes shared decision making to optimise healthcare services (Bravo et al. 2015; NICE, 2016b; ADA, 2016).

Several education structured educational programmes have been validated through research to ensure patient empowerment. These include the diabetes education and self-management for ongoing and newly diagnosed (DESMOND), the Diabetes X-PERT Programme, and Dose Adjustment for Normal Eating (DAFNE) programme. The X-PERT Programme has been delivered to over 250,000 participants up to the year 2016, while the DAFNE programme has

been delivered to almost 44,000 participants in 2016. Following the implementation of these courses, there have been significant improvements in adherence to treatment regimens. Other parameters such as increased knowledge of diabetes have been enhanced leading to positive changes in illness beliefs, significant weight loss, decreased odds of smoking, lower depression rates, positive changes in personal responsibility, and better glycaemic control (Plank et al. 2004; Davies et al. 2008; Deakin et al. 2006, 2011; Diabetes UK, 2015, X-PERT, 2017; NICE, 2016a).

Lifestyle choices such as dietary modification are still crucial in the management of diabetes. However, the NICE guideline (NG 17) encourages patients to access structured educational programmes that give them the requisite knowledge on carbohydrate counting. Advice on diet should tailor to individual needs and should target essential areas such as weight control and minimisation of cardiovascular risk factors (NICE, 2016a). Robust evidence exists on several associations between dietary modification and improvement in health quality, especially cardiovascular risk factors. For instance, there is the positive correlation between reduction in salt intake and reduction in blood pressure (Cappuccio et al. 2006; Zhao et al. 2009; Kyu Ha, 2014; Graudal, Hubeck-Graudal, & Gesche Jurgens, 2017), avoidance of excessive caffeine intake and reduction in blood pressure (Geleijnse, 2008; Mesas et al. 2011), reduction in excessive alcohol consumption and improvement of blood pressure (Roerecke et al. 2017; Stewart et al. 2008; Miller et al. 2007; Xin et al. 2001; Ueshima et al. 1993), physical exercise and reduction in cardiovascular risk (American Heart Association (AHA), 2017; Eijsvogels et al. 2016; Agarwal, 2012; Buttar, Li, & Ravi, 2005).

A meta-analysis by Kennedy et al. (2013) on the glycaemic benefit of exercise in type 1 diabetes was inconclusive, and other researchers reached similar findings (Lukács & Barkai, 2015; Colberg et al. 2015). However, specific individual factors are contributory to this conclusion such as dosing and timing of insulin doses, calorific intake before, during or after exercise, and increased risk of hypoglycaemia (Lukács & Barkai, 2015). There is still value in exercise with a reduction of cardiovascular risk, reduction in blood pressure, weight reduction, and improved well-being, hence its essential place in the management of T1D (Chimen et al. 2012). Recent evidence from Tikkanen-Dolenc et al. (2017) found that exercise ensures a reduction in the associated risk of early mortality and cardiovascular mortality in T1D patients.

Some authors have argued that the burden of lifestyle modification may predispose some patients to negative psychological and behavioural implications, for instance, the burden of repeated self-monitoring and regulation of food intake with multiple insulin doses may impact

on the quality of life in particular when severe hypoglycaemic or hyperglycaemic episodes occur (Gonder-Frederick, 2014; Larrañaga, Docet, & García-Mayor, 2011). An initial episode of severe hypoglycaemia can be a debilitating and disruptive experience. Recurrent episodes of hypoglycaemia also increase susceptibility to decreased hypoglycemic awareness that can result in loss of consciousness, or death (Kalra et al. 2013; Abdelhafiz et al. 2015). As CYP develop into adulthood, they are prone to the pressures of keeping the ideal body weight or body image. As a result, studies have found that they are at an increased risk of developing eating disorders. For weight loss they may engage in behaviours such as deliberate missing of insulin doses, splitting of insulin doses, or restriction of food, binging and purging, improper use of laxatives, and strict exercise regimens (Colton et al. 2015; Wilson et al. 2015; Grylli et al. 2003; Neumark-Sztainer et al. 1998). Following a review of the Diabetes Attitudes, Wishes and Needs (DAWN) study, it highlighted the need for individuals with T1D to have emotional support, family support and social support networks for the management of their condition (Funnell, 2006).

The diagnosis of T1D can be challenging in childhood for patients, parents and their caregivers who have to perform the daily management requirements some of which include multiple daily checks of glycaemic levels, administering appropriate insulin doses, ensuring appropriate dietary intake, monitoring physical activity and ensuring tight glycaemic control (Streisand, & Monaghan, 2014). A delicate balance of achieving the right glycaemic control is trying, as several factors are in play, some of which include the demands from the physical and neurological development of the child and the varying demands from unplanned outbursts of physical activities (Wood et al. 2013). Several other socio-emotional factors are contributory as the child develops, for instance, some parents perform the responsibility of educating support givers such as teachers and friends with the responsibility of being able to recognise early signs of hypo/hyperglycaemia. They also must be able to alter their schedule to respond to the needs of their child such as play dates and school activities. The child's emotional well-being may also impact on management. Some children view interventions from parents as an overbearing impingement on their autonomy. The resultant effect arising from multiple blood glucose checks can lead to needle phobia, and phobia for medical personnel or environments (Streisand, & Monaghan, 2014; Desrocher, & Rovet, 2004). For parents, drawing a balance between performing the normal daily routines, childcare and the additional routine of ensuring the right glycaemic control can lead to elevated stress levels (Williams, Laffel, & Hood, 2009). As the child attains adolescence, increasing autonomy is given to them in the management of their

condition, sometimes this period may be plagued with poor metabolic control because of the influence of family conflicts. Sometimes, the impact of increased autonomy of care may predispose them to increased pressures especially when they are introduced to self-management at an early stage without the requisite psychological maturity (Jaser, 2010; Palmer et al. 2004). Due to the peculiarity of the adolescence, and the resultant effects from the transition to early adulthood, they are at increased risk of disorders such as anxiety disorders, depressive disorders, eating disorders, and alcohol and substance abuse which impacts on metabolic control (Hood et al. 2006; Goebel-Fabbri, 2009). Crucial to successful psychosocial outcomes in management are strong family cohesion and support (Spencer, Cooper, & Milton, 2012).

The occurrence of psychiatric disorders in T1D may exist independent of T1D, as a complication of the condition, or as an independent risk of developing T1D. When these disorders are present, they predispose individuals to poor adherence to regimented treatment, inadequate metabolic control, increased complications, hospitalisations, and increased costs of care (Balhara, 2011; Butwicka et al. 2015). Evidence suggests an increased risk of developing mental health disorders in T1D (Almeida et al. 2018; Butwicka et al. 2015; Sivertsen et al. 2014).

Recent evidence suggests that the use of alcohol, smoking and substance abuse correlates closely with patterns and prevalence seen in the general population (Pastor et al. 2017; Hogendorf et al. 2016; Weitzman, Ziemnik, Huang, & Levy, 2015; Palladino et al. 2013; Cavoy et al. 2005). The pattern of alcohol, smoking and substance abuse use starts in teenage years and most times intensifies into young adulthood. Several factors may influence patterns of use in T1D; these include the increased stress of daily management of their condition, the possible influence of other mental health conditions, peer pressure, and possible effects of familiarity with injection techniques (Feltbower et al. 2008). The use of alcohol can initiate and potentiate conditions like anxiety disorders and depression. Substance abuse also correlates closely with the onset or potentiation of disorders like aggressive behaviour or violent outburst, self-harm, schizo-affective disorders and psychosis (Rehm et al. 2009). The resultant effect of excessive alcohol use and substance abuse is its ability to impair strict adherence to the treatment regime, thereby contributing to worsening metabolic, glycaemic control and onset of secondary complications (Pator et al. 2017; Sacco, & Bykowski, 2010). Smoking is seen to potentiate the increased risk of developing microvascular complication through its effect of causing endothelial dysfunction and increased inflammation. It is also known to potentiate the advent

and progress of cardiovascular complications hence leading to increased mortality (Eliasson, 2003; Hovind et al. 2003).

The relationship between poor health and poor socioeconomic indices are well documented, with a socioeconomic health gradient in which poorer members of society are prone to more substantial effects of morbidity and mortality in comparison to more affluent individuals (Grintsova, Maier, & Mielck, 2014; Brown et al. 2004). A systematic review by Scott et al. (2017) established that regardless of health systems, T1D patients exhibited similar findings of increased risk of morbidity and mortality for those with lower socioeconomic status. This is supported by findings from the study carried out by Rawshani et al. (2015).

1.7 Future challenges in T1D

T1D remains a condition that occurs through a complex interplay of genetic and environmental factors. Future trends in the management of this condition attempt to utilise several options to stem the rising incidence of T1D. One of the areas being investigated are possible interventions to prevent the onset of T1D. Two trials done were the European Nicotinamide Diabetes Intervention Trial (ENDIT), and the Diabetes Prevention Trial – type 1 (DPT-1) which observed no protective effects on the onset of T1D (Gale et al. 2004; Vehik et al. 2011). Several studies have been designed and are ongoing in different stages that target immunomodulatory mechanisms to influence either specific antigens or broad-based immune modulators all with limited success. They are designed to interfere with processes that activate pathogenic cells or enhance regulatory mechanisms.

Furthermore, some other studies were designed to alter metabolic or environmental determinants by altering nutritional component implicated in the onset of T1D. The overall aim of these studies was to slow down the onset of β-cell destruction while restoring self-tolerance. Some of which include nutritional therapies involving the use of Omega-3 fatty acids and vitamin D supplementation and Cow's milk protein administration (Tooley, Waldron-Lynch, & Herold, 2012). They have shown limited success; however, these trials have provided new insights into the possibility of using combination therapies targeting multiple pathologic pathways to harness the beneficial effects of the various single therapies. Other areas being examined include possible stem cell therapies in rejuvenating β-cell regeneration (Anzalone et al. 2011). Transplant therapies are available with success rates of almost 80% in the first year decreasing to 20% in the fifth year. Recent progress in transplanted procedures was made under the auspices of the Diabetes Research Institute in 2016 utilising insulin-producing cells within

a biological scaffold engineered onto the surface of the omentum. This procedure was a success as the recipient was able to achieve freedom from insulin therapy. This highlights advancement in transplant techniques through insights from bioengineering. Another area showing promise is the microencapsulation for cell therapy (Calafiore, 2018). Overall, two main strategies are on the horizon to tackle T1D; one is to establish interventions that prevent the onset of autoimmunity and second to establish therapy that limit the progression of autoimmunity as well enhance β-cell regeneration.

In summary, this chapter has critically explored the literature with regards to T1D. It has shown that T1D is associated with increase in premature or excess mortality, and as such there is a need to explore an overview of the current evidence on trends in mortality from T1D using a systematic review of evidence (see chapter 3). There is also the explore the factors that contribute to premature mortality in T1D by exploring the following aims and objectives.

Aims

This study aimed to identify predicting risk factors for mortality and survival in T1D in the Wirral.

Objectives

This study had the following objectives:

1. To evaluate factors relating to all-cause mortality, cardiovascular and non-cardiovascular mortality in T1D.
2. To conduct a systematic review and meta-analysis, in order to present current evidence of all-cause and cause-specific mortality amongst T1D patients.
3. To examine the role of variables such as socioeconomic status, smoking, body mass index, blood pressure measurements, glycaemic control, lipid profile, nephropathy, and retinopathy as predictive risk factors of mortality in the Wirral
4. To evaluate the influence of age at diagnosis, duration of diabetes, year of diagnosis and gender on mortality in the Wirral.
5. To evaluate survival, life expectancy and mortality patterns in T1D

The next chapter is the methodology chapter that explores methodological perspectives to the conduct of a retrospective cohort study. It further provides the procedural methods in the conduct of this study.

Chapter 2: Methodology

This chapter on methodology followed a logical description of how the study was carried out. It outlined the methodological approach and the methods employed throughout the study process. The conduct of any study is governed by the inherent philosophical principles adopted by the researcher; these are influenced by a set of beliefs or assumptions held by the researcher on the nature of reality, the relationship between the researcher and the researched and the

knowledge (Parahoo, 2006). Quantitative methodology was adopted to carry out this study; this methodology allows for empirical exploration of the phenomenon under investigation using statistical analysis.

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4. To evaluate the influence of age at diagnosis, duration of diabetes, year of diagnosis and gender on mortality in the Wirral.
5. To evaluate survival, life expectancy and mortality patterns in T1D

2.1 Methodology

Quantitative methodology allowed for numerical estimation of the total number of deaths in a cohort with T1D in the Wirral and the cause of mortality. Further statistical analysis allowed for the evaluation of several variables as predictive risk factors of mortality in T1D. Using the quantitative approach ensured that the observed mortality in T1D in the Wirral was reliably credited to the effects of the predictor variables without influence from biases (Creswell, 2013; Crossman, 2014; Jakobsen, 2013). For this study, quantitative methodology enabled for the use of statistical analysis, inferential statistics and hypothesis testing to arrive at results that could be generalized.

In carrying out this study, the ontological approach adopted was a positivist view of synthesis that follows a hypothetical-deductive process of research. The measurement of the observations in this study was based on the presumption that the objective reality as obtained from the

statistical analysis was independent of the views of human perception (Sale, Lohfeld, & Brazil, 2012). The observations (number and trends) of the dependent variable mortality were observed independent of predictor variables, this allowed for reliable estimate(s) of the causal relationship between exposures (predictor variables) and results observed (mortality) (Tuli, 2010; Jörg & Björn, 20007; Shanks, 2002). The epistemological view adopted in this research was an independent view of observations within this study without any direct influence on the variables. This enabled for valid observations of the estimates obtained. The ontological approach within this study was objectivism; the researcher was able to establish a causal relationship between the predictor variables and mortality. Axiological view in this study was to remain unbiased (Creswell, 2013).

The cohort study design was used to address the research aim in establishing the relationship between predictor variables and outcome measure (mortality). Although the use of any form of a descriptive study may have been appropriate to address the study aim by providing point estimate of mortality indices during the follow-up period. However, its use may not have provided any timeline of the cycle of events, making it difficult to ascertain or infer any causal relationship between the predictor variables and mortality (Webb & Bain, 2011; Bonita, Beaglehole, & Kjellström, 2006). The cohort study design was able to establish in chronological order the effects of the predictor variables on the outcome measure of mortality; it also allowed analysis to establish significant predictors of mortality (Webb & Bain, 2011; Levin, 2006; Mann, 2003).

For this study, the cohort study design was used to:

- Generate evidence on morbidity and mortality indices in T1D in Wirral peninsula
- Establish the association between the onset of T1D and progression of complications providing insight into the management of the condition.
- Generate composite outcomes in T1D such as all-cause mortality, cause-specific mortality, changes in morbidity, treatment effects, and disease-specific outcomes such as survival.

The conduct of cohort studies has the following inherent procedural characteristics (Hubert, 2014):

- The identification of a sample of participants (cohort), with or without a known exposure but at risk of developing a particular outcome of interest.

- The collation and analysis of data from the participants (cohort) with exposure to risk factors and outcomes measures over a period
- Drawing inference or associations between exposure and outcome measures

The essential design elements of cohort studies are:

- The development of a hypothesis to be tested
- Identifying the groups and subgroups of participants to be investigated
- Defining the exposure(s) of interest and its measures
- Measuring the confounders
- Defining the outcome(s) of interest and its measurement(s) including analysis
- Drawing inferences between exposure and outcome measures

The inherent design elements of cohort studies helped to address the research aim for this study in two dimension aetiological and prognostic dimensions (Herbert, 2014; Imamnovic, 2014).

In looking at the etiologic dimension to this study, for a cohort of participants with T1D, this study attempted to establish the causal associations between predictive risk factors and mortality in T1D, and the extent to which any of these factors modified mortality in T1D. This was based on the premise that one or several of the predictive risk factors could occupy the continuum that led to mortality in T1D and also that some of the predictive risk factors could potentiate, mediate, or have additive effects on the outcome of mortality (Hernán, & Robins, 2019; Steyerberg, 2009). In this study, the prognostic dimension was to estimate survival from T1D, considering the predictive risk factors. This was done by using statistical analysis to estimate the median survival times of various strata of the predictive risk factors. This had the advantage of identifying particular groups with poorer prognosis in T1D, with the potential of providing insight into preventive measures for these target groups (Grobbee & Hoes, 2015; Kaufmana, Kaufmanc, & Poolea, 2003).

This study followed a retrospective approach (sometimes referred to as historical cohorts) that involved the collation of pre-existing data on predictive risk factors individuals diagnosed with T1D and data on the outcome measure of mortality (Hubert, 2014; Grobbee & Hoes, 2015; Webb & Bain, 2011). This had the advantage of reduced cost during the data collation process. In this study, because the researcher was unable to influence allocation into subgroups, the study was able to identify incidence, prevalence, and mortality patterns, hence identifying the natural progression of T1D and mortality. Other advantages of cohort study as it applies to T1D are outlined in table 2.1 below.

Table 2.1: Advantages of cohort studies

- Establishes the temporal sequence between exposure and outcome measures such as the development of morbidity and mortality (Song & Chung, 2011)
- Establishes the direction of the temporal sequence observed (direction of causality)
- Enables indices that compute the effects of exposure outcomes to be calculated such as incidence rates, mortality rates, morbidity rates, relative risk and risk ratios [RR], attributable risk [AR], risk difference, and confidence intervals (Webb & Bain, 2011)
- Linked to essential steps in the estimation of hazard ratios [HR], survival analysis, and life table analysis (Lee et al. 2007; Hsu et al. 2017).
- Function to examine multiple effects of a single exposure as well as multiple exposures and effects.
- Facilitate the study of rare disease occurrences or conditions
- Generate hypotheses that can be further be evaluated by randomised control trials (Webb & Bain, 2011)
- Cohort study limits the bias attributed to knowledge of outcome status because, at the time of enrolment, study participants do not have the outcome measure evident.
- Cohort study ensures that data collection is accurate when it pertains to exposure, confounders and outcome measures.
- Cohort study can provide a time-efficient way of using existing data to provide answers or generate hypotheses to disease occurrence that are of increasing public health relevance

The landmark large-scale cohort study, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) highlighted the importance of tight glycaemic control to limit the onset and progression of complications in T1D (Nathan et al. 1993). However, this study noted that those on intensive therapy (INT) were at an increased risk of hypoglycaemic episodes (Nathan et al. 2014; Zinman et al. 2014). This provided further insight for this study as one of its objectives was to establish the risk of mortality according to various glycaemic levels; this helped to provide an insight into those that were at the highest risk of mortality so that targeted measures could be implemented at those with high risk.

In this study, some participants may be lost to follow up for reasons such as withdrawals, inadequate communication, and relocation from the study area. These factors may have affected the study results leading to over-or-underestimation of outcomes (Sedgwick, 2014). Cohort studies study can be affected by differential methods during the study such as changes in classification of diagnosis, measurement parameters, diagnostic procedures, and the

aetiology of death. These present difficulty in ensuring consistency in the measurement of outcome measures limiting the validity of results. In this study, one of such difficulty encountered was a change in the target levels for HbA_{1c} from ≤ 58 mmol/mol (7.5%) prior to 2015 to ≤ 48mmol/mol (6.5%) after 2015 (Song & Chung, 2010; Mann, 2003; NICE, 2015a, 2015b). Another difficulty encountered which limited impact on this study was a transition of from ICD-9 to ICD-10 for the classification of the aetiology of death during the study period.

Cohort studies are prone to several forms of bias. Bias is the tendency for a systematic error to occur in a study that limits the exact effect estimate in outcome measure(s) either during the design, conduct or during data analysis (Norvell, 2010; Grimes & Schulz, 2002). They include:

- Selection bias: a systematic error that occurs when the selection of participants into subgroups is based on inherent characteristics that may impact the results of outcome measures. To overcome the influence of selection bias in this study, participants for this study had to meet strict inclusion criteria.
- Confounding: evident when differing competing risks not accounted for during the study that interferes with the accurate effect estimate of results. One way to minimise the influence of confounding variables is by randomisation. The study design did not allow for randomisation of participants and also due to ethical consideration, however, to limit the impact of confounding an internally matched controls were identified that were closely identical to the exposed subjects (Sjölander, & Greenland, 2013; Faresjö, & Faresjö, 2010; Cummings, McKnight, & Greenland, 2003; Greenland, & Morgenstern, 1990).

Other methods employed to limit the influence of biases in this study was the use of multivariate analysis which employed a statistical approach to analysis that allows for the simultaneous consideration of several risk factors to establish the relationship between these variables (Chatterjee, Sinha, Diver, & Feigelson, 2010; Giroux, 2008; Breslow, 1985).

2.2 Methods

This section critically describes the methods used to collect and analyse data to answer this study research question. Some of the variables that were examined to answer the research objectives are the age at diagnosis, sex distribution, socioeconomic status, and cardiovascular implications. It examined a cohort of 1800 participants with T1D in the Wirral peninsula using data from the Wirral Diabetes Register [WDR]. The data was collected between December

2016 and March 2018. Diagnosis of the participants was made in primary or secondary care; the follow-up period was from January 1st, 2000 and December 31st, 2012.

The key areas that this section will address are:

- Description of Wirral peninsula, a setting in which the study took place
- The process of obtaining ethical approvals for the study
- Sampling methods and selection criteria
- The process of data collection and management
- Statistical techniques and analysis

2.2.1 Wirral Peninsula

The Wirral is a metropolitan district covering an area of approximately 15,704.63 hectares in the Northwest of England. It comprising 22 wards including Clatterbridge in the central axis, Caldy, Hoylake & West Kirby situated in the western axis, Wallasey in the northern axis, and Birkenhead in the eastern axis. The peninsula shares a boundary with Liverpool with an interjection from the River Mersey in the east. The river Dee separates it from Wales in the west while it is bordered to its north axis by the Irish Sea. It also shares a boundary with the county of Cheshire West and Chester in the south. The Wirral comprises of rural, semi-urban, urban, and industrial areas.

In 2016, the mid-year population estimates for the Wirral was 321,238, with females numbering 166,007 (51.7%) and males 155,231 (48.3%). These figures are extrapolations of the 2011 census figures, where Wirral had an overall population of 319,800, showing an overall increase of 1,438 between 2011 and 2016 (Office of National Statistics [ONS], 2017, Wirral Compendium of Statistics, 2017, Wirral Compendium of Statistics, 2012, Wirral Joint Strategic Needs Assessment [JSNA], 2012). The proportions of males in Wirral are lower than estimates obtained for England and United Kingdom estimates, while the proportions of females in England and UK are lower. Table 2.2 highlights comparisons between Wirral, England and UK estimates.

Table 2.2: Comparison of the Wirral, England and UK Estimates of Mid-Year Population Estimates 2016 (adapted from Wirral Compendium of Statistics, 2017 and ONS, 2017).

The annual population growth in the UK is 0.8%; Wirral is noticing an annual population growth of 0.11%, which is higher than the national average of 0.8%. A projection of this notable increase is in the age groups above the age of 65 years. Estimates project an overall increase in the population of Wirral from 321,238 in 2016 to approximately 330,800 in 2035. Population estimates for 2016 showed that the age group with the highest population was the 50- 54-year-olds, with a projected contraction for population estimates in the age groups between 15 – 29 years from 2016 to 2035 (Wirral Compendium of Statistics, 2017). Table 2.3 highlights the 2016 population breakdown into age groups.

	Wirral	**England**	**United Kingdom**
Total population	321, 238	55, 268, 067	65, 648, 054
Males	155, 231 (48.3%)	27, 300, 920 (49.4%)	32, 377, 674 (49.3%)
Females	166, 007 (51.7%)	27, 967, 147 (50.6%)	33, 270, 380 (50.7%)

Ethnicity: Ethnic configurations in the Wirral showed that the White-British were the primary ethnic group resident in this area. They accounted for 95.7% of the total population as compared to the national average of 92.1% (ONS, 2017). Other ethnicities extant within the populations include White-Irish, White and Black Caribbean, Black Africans, Asians and Other Mixed Ethnicities.

Table 2.3: Estimated Resident Population by 5-Year Age Group and Gender Wirral, Mid-2016. (Adapted from Wirral Compendium of Statistics, 2017).

Age Group	**Males**		**Females**		**Persons**	
	Number	**%**	**Number**	**%**	**Number**	**%**
0-4	9,853	3.1%	9,143	2.8%	18,996	5.9%
5-9	9,838	3.1%	9,492	3.0%	19,330	6.0%
10-14	9,292	2.9%	8,843	2.8%	18,135	5.6%
15-19	9,284	2.9%	8,695	2.7%	17,979	5.6%
20-24	8,352	2.6%	7,832	2.4%	16,184	5.0%
25-29	9,188	2.9%	9,539	3.0%	18,727	5.8%

30-34	8,652	2.7%	9,368	2.9%	18,020	5.6%
35-39	8,398	2.6%	9,333	2.9%	17,731	5.5%
40-44	9,287	2.9%	10,074	3.1%	19,361	6.0%
45-49	10,993	3.4%	11,805	3.7%	22,798	7.1%
50-54	11,472	3.6%	12,647	3.9%	24,119	7.5%
55-59	10,709	3.3%	11,462	3.6%	22,171	6.9%
60-64	9,476	2.9%	10,255	3.2%	19,731	6.1%
65-69	10,175	3.2%	10,579	3.3%	20,754	6.5%
70-74	7,631	2.4%	8,432	2.6%	16,063	5.0%
75-79	5,506	1.7%	6,931	2.2%	12,437	3.9%
80-84	3,932	1.2%	5,483	1.7%	9,415	2.9%
85-89	2,253	0.7%	3,703	1.2%	5,956	1.9%
90+	940	0.3%	2,391	0.7%	3,331	1.0%
All Ages	**155,231**	**48.3%**	**166,007**	**51.7%**	**321,238**	**100.0%**

Socioeconomic Indices: A measure of the prevalent social and economic status of a particular area can be obtained from an assessment of the index of multiple deprivations (IMD). IMD is a ranking that assesses seven distinct domains to ascertain unmet needs secondary to the lack of resources (Wirral Intelligence Service, 2016). The Wirral peninsula ranked 66th position in the year 2015, just one ranking above the 65th position, which is considered to be among the 20% most deprived authorities in England. However, spatial disparities exist in some regions of the Wirral, with Birkenhead being the most deprived. Although study highlights the links between poverty and ill health, this study has one of its aims as assessing the relationship between socioeconomic status, glycaemic control and impacts on mortality making such disparities important to this study.

Life Expectancy in the Wirral: Life expectancy refers to a statistically derived average number of years an individual in a particular cohort is expecting based on current estimates of age-specific mortality rates of that cohort (WHO, 2003; Mathers et al. 2014). The process of estimation involves survival analysis using either period or cohort life tables. The life expectancy in the Wirral shows a marginal improvement over time but remains lower than those for England. Tables 2.4 and 2.5 show life expectancy for males and females in Wirral for 2011 – 2013 were 77.8 years and 82.3 years respectively, compared to England with an average of 78.9 years and 82.7 years for males and females respectively (Wirral Compendium of Statistics, 2017, ONS, 2016).

Table 2.4Trend in Life Expectancy at Birth with 95% Confidence Limits, Wirral, 1998-2000 to 2013-15 (adapted from Wirral Compendium of Statistics, 2017)

Period	**Males**		**Females**	
		95% Confidence Intervals		**95% Confidence Intervals**

	Life Expectancy (Years)	Lower Limit	Upper Limit	Life Expectancy (Years)	Lower Limit	Upper Limit
1998-2000	73.9	73.5	74.3	79.2	78.8	79.6
1999-2001	74.3	73.9	74.7	79.7	79.3	80.0
2000-2002	74.9	74.5	75.3	79.9	79.6	80.3
2001-2003	75.2	74.8	75.6	80.0	79.7	80.3
2002-2004	75.4	75.0	75.8	80.2	79.8	80.5
2003-2005	75.6	75.2	76.0	80.3	79.9	80.6
2004-2006	75.8	75.4	76.2	80.8	80.4	81.1
2005-2007	75.9	75.5	76.3	81.0	80.6	81.3
2006-2008	76.2	75.8	76.6	81.0	80.7	81.4
2007-2009	76.6	76.2	76.9	81.0	80.6	81.4
2008-2010	77.3	77.0	77.7	81.0	80.6	81.3
2009-2011	77.6	77.2	78.0	81.7	81.3	82.0
2010-2012	77.9	77.6	78.3	81.9	81.6	82.2
2011-2013	77.8	77.4	78.2	82.3	82.0	82.7
2012-2014	78.0	77.6	78.4	82.2	81.8	82.5
2013-2015	77.9	77.6	78.3	81.9	81.5	82.2

Table 2.5: Trend in Life Expectancy at Birth with 95% Confidence Limits, Wirral, 1998-2000 to 2013-15 in comparison with England (adapted from Wirral Compendium of Statistics, 2017; ONS, 2017)

Period	Males (life expectancy Wirral)	Males (life expectancy England)	Females (life expectancy Wirral)	Females (life expectancy England)
1998-2000	73.9	76.01	79.2	80.66
1999-2001	74.3	76.24	79.7	80.72

2000-2002	74.9	76.55	79.9	80.91
2001-2003	75.2	76.90	80.0	81.14
2002-2004	75.4	77.32	80.2	81.55
2003-2005	75.6	77.65	80.3	81.81
2004-2006	75.8	77.93	80.8	82.02
2005-2007	75.9	78.30	81.0	82.30
2006-2008	76.2	78.40	81.0	82.60
2007-2009	76.6	78.00	81.0	82.09
2008-2010	77.3	78.31	81.0	82.33
2009-2011	77.6	78.71	81.7	82.68
2010-2012	77.9	79.02	81.9	82.83
2011-2013	77.8	79.21	82.3	82.96
2012-2014	78.0	79.35	82.2	83.05
2013-2015	77.9	79.38	81.9	83.00

The specific research setting for this study was The Wirral University Teaching Hospital Foundation Trust (WUTH) is the resident custodian of the Wirral diabetes register. WUTH delivers healthcare services to people of the Wirral Peninsula and its environs extending to the North West of England and North Wales.

Wirral Diabetes Register

The process involved the identification of all T1D patients in the Wirral Diabetes register up until December 2012. This register operated from 1997 to May 2013 and contained data of patients diagnosed with diabetes (T1D and T2D), from both primary and secondary care. However, the register began winding down to closure from December 2012. This register was an electronic register that had linkages to parameters such as age at diagnosis, demographics, socioeconomic status, biochemical profiles such as HbA1c, lipid profiles and renal status. These parameters were used to evaluate their relationship to morbidity, mortality and life expectancy in various subgroups. Where possible, medical notes were retrieved to obtain any other outcomes of interest.

It had its origins when the UK subscribed to the 'St. Vincent declaration' of 1990. This set the tone for which the labour government of 1999 produced the National Service Framework [NSF] Standards (2001), which was essential in the management of diabetes. The National Service Framework delivery Strategy (2002) proposed measures to be attained within ten years proffered by the NSF standards. These strategies included the setting up of disease registers, implementation of eye screening, upscale of support services and implementation of system-

wide diabetes therapeutic regimens (DOH, 2002). The Wirral Diabetes Register, which ran from 1997 to early 2013.

The term register as defined by the Dictionary of Epidemiology is

"A file of data concerning all cases of a particular disease or other health-relevant condition in a defined population such that the cases can be related to a population base…If these cases are regularly followed up, information on remission, exacerbation, prevalence, and survival can also be obtained" (Porta et al. 2009, pg. 243).

The adequate management of any long-term condition is dependent on the establishment and optimum functioning of an accurate well-maintained register. Historical perspectives suggest the White Paper '*Saving Lives: Our Healthier Nation'* supported the introduction of disease registers to strengthen the information resource available on chronic medical conditions in the UK. The duty of setting up and maintaining disease registers was entrusted to primary care trusts (Newton & Garner, 2002).

The Wirral Diabetes Register had the following functional objectives:

- Ensure optimum levels of patient care, whereby information garnered provided the basis for regular recall and review of management, providing structured individualist care, risk assessment and stratification, and regulating access
- Application to public health where data from the register was used for disease surveillance, planning for the allocation of resources, assessing the impact of preventive measures and estimating the burden of the disease
- Regular update and appraisal of the register to ensure that technology assessment was regularly updated keeping it at pace with technology improvements
- Provide a basis for research to be carried out, generation of hypotheses, improvement of study designs, and analytic study

To ensure that the WDR was a valid register, it had to conform to laws that governed confidentiality, data protection and security such as the 'EU Data Protection Directive 1995', 'Data Protection Act, 1998', 'Health and Social care Act 2001', and Human Rights Act 1998. It also had to conform to guidance such as the NHS policy on Confidentiality, Medical Research Council guidance, and the General Medical Council Guidance (Newton & Garner, 2002). The register was set up with collaboration from primary, secondary, and community

care services with strict adherence to confidentiality and security. Database administrators updated changes to patient data such as updates on various parameters, co-morbidities, and changes of address. A WDR was a unique database that became a central repository with several linkages; a unique patient identification number assigned (PIDN) to each patient at the point of diagnosis was linked to the electronic patient health record (EPR). The EPR using the PIDN contained records of NHS numbers, the date of confirmation of diagnosis, biophysical, and biochemical parameters, links to the laboratory, GP, hospital, eye screening and supportive services such as podiatry.

The register is an electronic register under the custody of the Wirral University Teaching Hospital NHS Foundation Trust. The central identifiers used to recognise patients were their NHS number, hospital number and Personal Identification numbers (PIDNs). The informatics department did linkages between the various sources of data. The collation of data from various sources ensured that the process of data collection was comprehensive, data collation from primary and secondary care provided robust evidence in accurately predicting risk associated with T1D.

2.2.2 Ethical approvals

Ethical approval for this was sought from the University of Chester (PhD study base) and Wirral University Teaching Hospital (custodian of the Wirral Diabetes Register). Also, consent was also sorted for IRAS ethics approval. However, after reading the study protocol, the Trust decided that IRAS ethics approval was not required. Trust research and development unit provided permission to access and use the data (letter attached in the appendix).

2.2.3 Data Collection and Handling

Records from the register were collated between 1997 and 2012. These records were stored on dedicated servers under the auspices of WUTH. Data for this study were extracted from the database between December 2016 and March 2018. Supplementary data was collected by gaining access to case notes. These case notes were accessed weekly in batches of between 20 to 30 case notes at a time from records kept at a storage location in Manchester. Due to data protection, data was kept for eight years after death and then destroyed. This created a study limitation because once the 8-year period had elapsed access to the information in case notes were lost which meant that data regarding the cause of death from some participants in the study could not be retrieved.

The process of data collection entailed extracting data from the register into an excel spreadsheet in preparation for data analysis. The data extracted included the following; Patient's Personal Identification numbers (PIDNs), NHS number, gender, date of birth, age at diagnosis, confirmation status of the patient, weight and height. Other information included eye screening status, baseline, average and most recent values for HbA_{1c}, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine, albumin, cholesterol, triglycerides, HDL, LDL, thyroid stimulating hormone (TSH), smoking and alcohol intake. Data on cause of mortality was obtained from retrieved case notes and triangulated with online data from the General Register Office.

2.2.4 Data validity

This database was used for a similar PhD project studying the Type 2 diabetes cohort, during which the IT department checked that the process of validation had been carried out yearly to ensure the accuracy of data used. This process involved the removal of invalid data, retrieving more data from laboratory services, updating mortality status and date of death. The IT department regularly did quality assurance and data integrity. This was to ensure that the data uploaded from the various sources met the set procedures for the establishment of the register. The measures used were data encryption and access controls to ensure no unwanted access, including imposed restrictions of read-only and write privileges to sections of the database. Data backup was in place as alternate servers provided backup and input validation to ensure that incorrect data was not inputted into the database. Data validation ensured high-quality transmission of data without corruption from the sources. Outlier values were deleted, and no coding changes occurred throughout the existence of the register (Gliklich Dreyer, & Leavy, 2014).

In this study power and sample size calculation was performed in order to ensure that the differences between the variables under consideration are accurate thereby avoiding type II error (Hulley et al. 2013; Chow, Shao & Wang, 2008; Jones, Carley, & Harrison, 2001). One constraint to ascertaining the sample size was the limited number of T1D participants in this cohort from the database. However, to ensure the sample size was sufficient to create an adequate effect estimate, a consideration of the sample sizes of a systematic review looking at mortality in T1D was used for the power calculation. The review had six cohort studies done in the UK, with sample sizes varying from 128 to 25,752 participants. Two of the studies included used registers of T1D and had populations of 828 and 1,854 participants. To estimate a sample size between 1000 and 1500 was, therefore, an appropriate sample size for this study

(Edge, Ford-Adams, Dunger, 1998; Liang et al. 2003; Robert et al. 2004; Swerdlow et al. 2004).

The power of this study was dependent on the variables being measured. Below is the probable power (effect size) calculation for this study with an approximate number of 1300 participants using the means effect sizes. Instead of taking the effect size as the input and calculating the group sizes, this calculation took the group sizes as inputs and calculated the effect size that the study had (1 - β) power to detect. The effect size was then calculated in two different ways: first using the T statistic (with a non-centrality parameter), then using the Z statistic. The Z statistic approximates the T statistic but provides an effect size that is slightly too small. However, the Z statistic calculation was considered appropriate because it allowed comparison with other calculators that use the Z approximation.

$\alpha\ (two - tailed)\ =\ 0.05$ *Threshold probability for rejecting the null hypothesis. Type I error rate.*

$\beta\ =\ 0.2$ *Probability of failing to reject the null hypothesis under the alternative hypothesis. Type II error rate.*

$Total\ group\ size\ =\ N_{total}\ =\ N_1\ +\ N_0\ =\ 1300$

The proportion of subjects in Group 1 $(q_1) = N_1/N_{\ total} =\ 0.846$

Proportion of subjects in Group 0 $(q_0) = 1 -\ q_1\ =\ 0.154$ where q1 is Proportion of subjects that are in Group 1 (exposed) and q_0 is the proportion of subjects that are in Group 0 (unexposed); 1-q1

1. Calculation using the T statistic and non-centrality parameter:

Degrees of freedom $(DoF) =\ N_{total} - 2\ = 1298$

The standard T value corresponding to α $(T_\alpha) = 1.962$

Where K is the non-centrality parameter, E is the effect size, and S is the standard deviation of the outcome in the population.

$k = \sqrt{\left({}^{1}/_{N_1} + {}^{1}/_{N_0}\right)} =\ 0.07687K$

Non-centrality parameter $(\delta)\ =\ 2.80371$

$E/_S = k * \delta = 0.21552$

This study has 80.0% power to detect an effect size of

$\boldsymbol{E = S * E/_S = 0.804}$

2. Normal approximation using the Z statistic instead of the T statistic:

Standard normal deviate for $\alpha = Z_\alpha = 1.95996$

Standard normal deviate for $\beta = Z_\beta = 0.84162$

$A = (Z_\alpha + Z_\beta)^2 = 7.84887$

$B = 1/q_1 + 1/q_0 = 7.68182$

$C = AB/N_{\text{total}} = 0.04638$

$E/_S = \sqrt{C} = 0.21536$

This study has 80.0% power to detect an effect size of

$E = S * E/_S = 0.803$

Because the formula used here is based on approximating the T statistic with a Z statistic, it slightly underestimated the effect size for smaller values of N_{total} (Hulley et al. 2013). Hence, the total number of 1300 participants was required for 80% power for this study.

2.2.5 Hypothesis testing

This study examined the following hypothesis:

Null Hypothesis H_0: There will be no significant difference in mortality in T1D by the impact of the predictor risk factors except that due to chance.

Alternate Hypothesis H_1: The predictor risk factors will predict mortality in T1D

2.2.6 Eligibility criteria

Inclusion

Participants were included in the study if they met the following criteria:

- Diagnosis of T1DM confirmed by healthcare practitioners in primary and secondary care and registered in the register
- Patients who were commenced on insulin therapy at diagnosis.

Exclusion

- Patients with T2DM confirmed and registered in the register

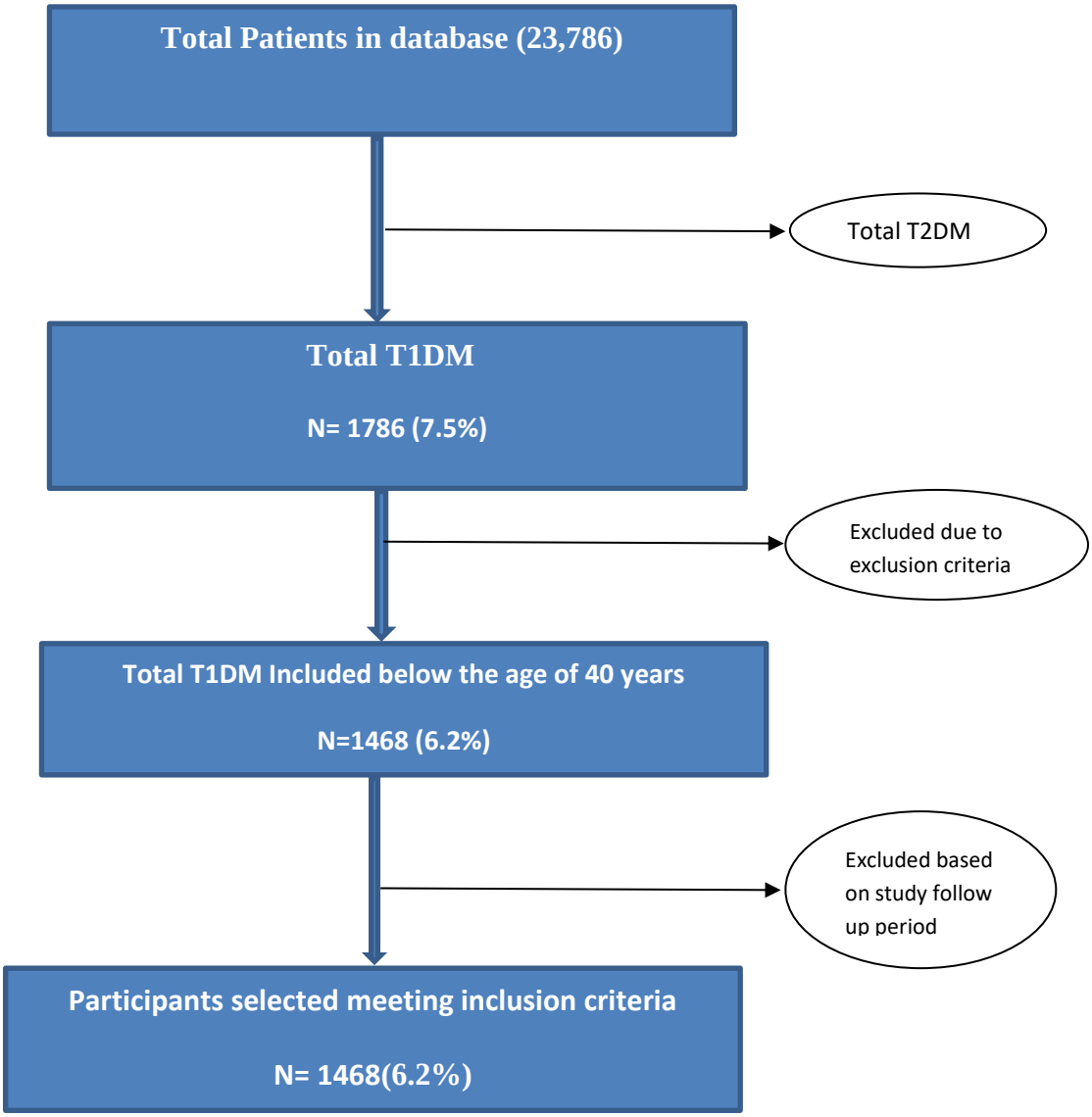


Figure 2.1: Study flow chart

2.2.7 Measurement of Clinical Parameters

The measurement of various outcomes of interest biochemically was done using the cobas® 8000 modular analyser series. The 8000 series modular platform is a high volume analyser capable of conducting 2000 test/hour comprised of four units. The platform consists of a core unit, high volume clinical chemistry modules (Cobas c 701 module and Cobas c 702 module), medium volume clinical chemistry module (Cobas c 502 module) and an immunoassay module (Cobas e 602 module).

The process of analysing plasma glucose was the enzymatic hexokinase method of phosphorylation of glucose in the Cobas analyser CLUC3 (McGlothlin, & Jordan, 1975; Junge, Wilke, Halabi, & Klein, 2004). The measurement of HbA1c utilised an automated ion-exchange chromatographic method (HPLC). The units to which HbA1c was reported in the DCCT trial served as a reference for reporting in this study. The results were standardised by the *International Federation of Clinical Chemistry* (IFCC) using the formula:

$$IFCC\ unit\ HbA1c\ (mmol/mol)\ =\ [DCCT\ HbA1c\ (\%)\ -2.15] \times 10.929$$

Serum creatinine was initially measured using alkaline picrate (Jaffe) method and then underwent a method of enzymatic and high-performance liquid chromatography (HPLC) which was standardised using an isotope dilution mass spectrometry (IDMS) (Delanghe, & Speeckaert, 2011).

The enzymatic colourimetric method was used to assay levels of total cholesterol (TC). The Friedewald equation was used to ascertain levels of LDL

$$LDL\ =\ (total\ cholesterol - HDL\ cholesterol - total\ triglyceride) \div 2.19$$

The Cobas Core Immunoassay analyser is the automated system used to assay levels of TSH; it utilises a big bead EIA technology (Michotey et al. 1995).

2.2.8 Measurements during clinic sessions

Clinic sessions involved initial checks and records of weight, height, and blood pressure. The automated BP machine (Omron T4) was used in BP measurements. Clinic sessions also involved the confirmation of demographic parameters of age, sex, address, smoking and alcohol status. Obtaining IMD scores from postal codes was done electronically, extracted from the Department for Communities and Local Government website.

2.2.9 Handling missing data and dropouts

Missing data is defined as data value not recorded for a variable of interest in a set of observations of interest. Handling of missing data is essential as poor handling of this aspect of research can affect the conclusions drawn from data analysed (Kang, 2013; Graham, 2009). For this study, the definition of missing data was unrecorded data in more than two places for age at diagnosis, age at death and duration of diabetes. Dropouts for this study refer to data for participants for which all variables are missing. The approach to handling missing data was to statistically use Little's Missing at Random Test (MCAR) for random missingness (Lindsey,

2000). Instead of excluding missing values in a listwise approach, the decision was to incorporate this data because of information from other non-missing variables for participants. This was to preserve the analytic robustness of the data (Diggle, & Kenward, 199; Little, 1995; Kang, 2013).

Missing data were as follows: gender (128), HbA1c (382), Creatinine (203), Cholesterol (332), Triglycerides (277), HDL (516), LDL (376), TSH (264), SBP (523), DBP (523), and BMI (555).

2.2.10 Measurement of parameters and Definition of Variables

The variables of interests that were measured during this study were gender, age and year of diagnosis, duration of diagnosis, age at death, and the year at death. Others were BMI, TSH, TG, HDL, LDL, DBP, SBP, serum creatinine, HbA_{1c} and mortality status.

Lipids profile

Lipids are defined as a subset of essential fatty acids involved in several functions such as the stabilisation of biological membranes, hormone transport and receptor signalling. Biochemically, they are measured to approximate the risk of development of cardiovascular disease (Orozco-Beltran et al. 2017). The parameters measured in the lipid profile test are total cholesterol; Low-density lipoprotein (LDL) cholesterol in high amounts deposit in the intima layer of blood vessels precipitating atherosclerosis and increasing the risk of developing cardiovascular disease. High-density lipoprotein (HDL) cholesterol aids in the transport of cholesterol from blood vessels back to storage in the liver as well as other regulatory functions. High levels of HDL are regarded as being protective and has an inverse correlation to the risk of developing cardiovascular disease (Ridker et al. 2010). Triglycerides are essential for energy production. However, very high levels are a risk factor for the development of cardiovascular diseases. The European Atherosclerosis Society Consensus Panel (2013) and the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of dyslipidaemia in Adults (Adult Treatment Panel III) (2002) specify lipid profiles and their categorical risk values as shown in Table 2.6.

Table 2.6: Lipid profiles and categorical risk for the general population including T1D

Risk Categories	**LDL Cholesterol** (mmol/L)
Optimal	≤ 2.59
Near optimal	2.59 - 3.34
Borderline high	3.37 - 4.1

High	4.15 - 4.90	
Very high	≥ 4.90	
Risk	Total Cholesterol (mmol/L)	
Desirable	≤ 5.18	
Borderline high	5.18 - 6.18	
High	≥ 6.22	
Risk	TG (mmol/L)	
Desirable	≤ 1.70	
Borderline high	1.7 - 2.2	
High	2.3 - 5.6	
Very high	≥ 5.6	
Risk	Non-HDL Cholesterol (mmol/L)	
Optimal	3.37	
Above optimal	3.37 - 4.12	
Borderline high	4.15 - 4.90	
High	4.9 - 5.7	
Very high	≥ 5.7	
HDL Cholesterol (mmol/L)		
Risk	Males	Females
Low level, increased risk	≤ 1.0	≤ 1.3
Average level, average risk	- 1.3	1.3 - 1.5
High level, less than average risk	≥ 1.55	≥ 1.55

Treatment recommendations from the NCEP Adult Treatment Panel III guidelines suggest that levels of LDL remain essential in mitigating the development of cardiovascular complications and management if individuals have the following:

- ≤ 2.59 mmol/L with diabetes or cardiovascular condition
- ≤ 3.37 mmol/L with 2 or more risk factors
- ≤ 4.14 mmol/L with 0 or 1 risk factor

TC/HDL and LDL/HDL ratios also play essential roles in the onset and prognosis of cardiovascular conditions (Reeder et al. 1997; Wang et al. 2002; Genest, Frohlich, Fodor, & Mcpherson, 2003; Gambardella et al. 2011; Qing-Jie et al. 2016). The categorisation of associated risk is shown in Table 2.6, 2.7 and 2.8.

Table 2.7: Lipid Profiles (TC/HDL-C) of the general population including T1D and associated risk of developing cardiovascular complications for both men and women.

TC/HDL ratio		
Risk category	**Men**	**Women**
Very Low	<3.4	< 3.5
Low	4.0	3.8
Average	5.0	4.5
Moderate risk	9.5	7.0

High Risk	>23	>11

Table 2. 8: Lipid Profiles (LDL/HDL) among male and female that are associated with the risk of cardiovascular complications in the general population including T1D.

LDL/HDL ratio		
Risk categories	**Men**	**Women**
Very Low	1.0	1.5
Average risk	3.6	3.2
Moderate risk	6.3	5.0
High risk	8.0	6.1

Table 2.9: Lipid ratios (TC/HDL LDL/HDL) among male and female that are associated with the risk of cardiovascular complications in the general population including T1D.

Ratio	**Primary prevention**				**Secondary prevention**			
	Risk level		**Target**		**Risk Level**		**Target**	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
TC/HDL	>5.0	>4.5	<4.5	<4.0	>4.0	>3.5	<3.5	<3.0
LDL/HDL	>3.5	>3.0	<3.0	<2.5	>3.0	>2.5	<2.5	<2.0

Serum creatinine levels

Serum creatinine levels serve as an essential variable in the assessment of kidney function. It is used to estimate the glomerular filtration rate (GFR) which assesses kidney function. Elevated creatinine levels are an indication of worsening renal function. A level of creatinine ≥ 177μmol/L is an indication of nephropathy (Baumgarten, & Gehr, 2011; Mendelssohn et al. 1999). One of the complications of T1D is diabetic nephropathy and manifest in its earliest form as microalbuminuria. This is evident in approximately half of all patients with T1D and occurs at a rate of 3% annually. The progression of diabetic nephropathy leads to chronic renal failure and end-stage renal failure manifesting biochemically with abnormal creatinine and glomerular filtration rates (GFR). Diabetic nephropathy is a risk factor for the development of cardiovascular complications and all-cause mortality in T1D (Daniels et al. 2013; Parving, & Hommel, 1989). Although the standard estimate for kidney function is obtained from the eGFR - Estimated glomerular filtration rate, due to the historical nature of the database, values obtainable were creatinine level, hence it use as a proxy for kidney function.

Table 2.10: Normal creatinine levels and albumin: creatinine ratio in the general population including T1D

Gender	The normal range of creatinine levels (µmol/L)
Male	44 – 80
Female	62 - 106
Albumin creatinine ratio (mg/mol) normal values	
Males	Females
< 25	< 35

Body Mass Index (BMI)

The WHO (2016) defines the Body Mass Index (BMI) as a simplistic assessment of weight-for-height. It is estimated by dividing the weight in kilograms by the square of the height in metres (Kg/m^2). It is the measure of classification of underweight, overweight and obesity in adults. The measurement of this parameter was important because of its correlation as a risk factor for the early onset of T1D (Abbasi et al. 2017; de Vries et al. 2014; Giménez et al. 2007).

Table 2.11: Body mass index (BMI) classification in the general population including T1D

Classification	BMI (Kg/m^2).
Underweight	< 18.5
Normal range	18.5 -24.99
Overweight	≥ 25.00
Pre-obese	25.00 – 29.99
Obese class I	30.00 – 34.99
Obese class II	35.00 – 39.99
Obese class III	≥ 40
The international classification of adult underweight, overweight and obesity according to BMI : (Adapted from WHO 2017)	

The IMD (index of multiple deprivations)

It is a variable that represents a measure of relative deprivation from some regions of the country referred to as Lower Super Output Areas (LSOA). These areas are fixed statistical locations assigned by the ONS having approximately 1500 people. In England, IMD ranks these small areas from 1 to 32,844 which corresponds from most deprived to the least deprived. IMD is a measure extrapolated by evaluating 37 indicators categorised into seven domains with differential weighting. These are Income Deprivation (22.5%), Employment Deprivation (22.5%), Education, Skills and Training Deprivation (13.5%), Health Deprivation and Disability (13.5%), Crime (9.3%), Barriers to Housing and Services (9.3%), and Living Environment Deprivation (9.3%). The postcodes of individual participants in the study were allocated to LSOA, for which their respective IMD score was extrapolated. These were classified into quintiles from 1 [most deprived] to 5 [least deprived] (Abel, Barclay, & Payne, 2016; Newton et al. 2015).

2.2.11 Death Ascertainment

Records of mortality as inputted in the register were triangulated with case notes that could be retrieved and with data from the online database of the general register office. The input of mortality statistics followed a standardised format that had the following details date of birth, sex, NHS number, and date of death. These parameters were anonymised for analysis; NHS number was required for matching data but deleted for analysis.

Cause of mortality status as recorded in the case notes utilised classification from the International Classification of Diseases (ICD), Tenth Revision [ICD-10]. ICD-10 classifies cause of death into a grid system. This classified some causes of death with the following codes Diabetes (E10 - E14), Septicaemia (A40-A41), Cancer (C00-C97), Acute myocardial infarction (I21 - I22), and Cerebrovascular disease (I60 - I69). In cases where the cause of death was inconsistent, records from the general register office were preferred. Records of diabetes as the direct cause of death is significantly lower at 39%, even though it contributes significantly to other causes of death such as cardiovascular syndromes (McEwen et al. 2006). Recommendations from ICD suggest that diabetes can be regarded as the principal cause of death if mortality was secondary to its complications (hypoglycaemia and other metabolic complications). Table 2.12 elaborates on causes of death into an item list as identified from the WDR.

Table 2.12: International Classification of Diseases, Tenth Revision [ICD-10], causes of death and codes

Item List	Cause of death	ICD-10 classification
1	Diabetes	E10 - E14
2	Cerebrovascular disease	I60 - I69

3	Septicaemia	A40-A41
4	Cancer	C00-C97
5	Acute myocardial infarction	I21 - I22
6	Other major cardiovascular diseases	I71 - I78
7	Pneumonia & influenza	J09 - J18
8	Chronic lower respiratory diseases	J40 - J47
9	Chronic liver disease & cirrhosis	K70, K73 - K74
10	Renal failure	N17 - N19
11	Heart disease	I00 - I09, I11, I13, I20 - I51
12	Alzheimer's disease	G30
13	Other infections and parasites	A00-A09, A20-A39, A42-A49, A54-A99, B00-B19, B25-B99
14	Other accidents & adverse effects	V01, V05 - V06, V091, V093 - V099, V10 - V11, V15 - V18, V193, V198 - V199, V800 - V802, V806 - V809, V812 - V819, V822 - V829, V879, V889, V891, V893, V899, V90 - X599, Y85 - Y869
14	Parkinson's disease	G20 - G21

2.2.12 Allocation of Comparison group

This study-utilised comparison groups from the resident population in the cohort database, local population estimates from the Wirral, and the national population estimates for the years within the study period. The national population estimates were used as controls and were estimated from mid-year estimates of England and Wales for the period under consideration. The local population estimate used for comparison was computed by deducting the TID population from the local Wirral population estimates at the time. The use of the resident population (internal comparison) within the cohort ensured the closest possible match in patient characteristics. This method of comparison provides a unique perspective of comparison for ascertaining the temporal sequence between exposure and outcome measures. For T1D, it helps to explore multiple outcomes with relative ease, accessibility to data, and less expensive in approach. To allow for the use of the general population for comparison, adjustments had to be made by stratifying the population according to gender, age, socioeconomic status, and other confounding variables. In assessing the use of the general population, it was necessary to note that a minute number of people in the general population who were unexposed could be liable to exposure to T1D as the period of study progressed. This had the impact of limiting the precise effect estimates for this study. Standardised mortality rates were used to quantify the magnitude of the association.

2.2.13 The process of data management and data analysis

The process of data analysis had a preparatory stage of data management that involved setting up the database into an appropriate format, in preparation for analysis. This involved the selection of the appropriate parameters or conversion to the required format for analysis. For scientific quality and integrity of data extrapolated from the database, it was essential first to categorise data with specified variables as follows

- Predictor or outcome variables: Mortality status, development of retinopathy
- Intervening variable (mediating variable): referred to as the possible variable used to explore the causal link between variables, this was the diagnosis of T1D.
- Independent or Explanatory variables: defined as a variable the has a possible influence on the outcome variable. In this study, these variables were gender, age, age at diagnosis, duration of diabetes, age at death, BMI, smoking status, HbA_{1c}, TC, TG, LDL, HDL, TSH, SBP, DBP.

The next stage was to ensure the data met the required scale of measure in preparation for input into the required statistical package. This was to determine if the variable to be inputted was a nominal, ordinal, or a scale variable. The nominal variables were categorical variables, having no kind of order and inputted as string or numeric equivalents; an example was sex. The ordinal variables referred to variables that had possible order example were smoking and IMD. The scales variables had origin; order and interval, some variable represented accordingly were BMI and HbA_{1c}. All data were classified as nominal, ordinal or scale variable.

The Statistical Package for the Social Sciences (SPSS) IBM software Version 24 was used for statistical analysis. Step in ensuring the appropriateness of data for analysis by SPSS included the following:

- Descriptive statistics for appropriate variables which included minimum and maximum values, mean, median, variance, range, interquartile range, variance and standard deviation
- Incidence analysis for categorical variables
- Test for normality and homogeneity for appropriate variables
- Recognising and tackling missing values and outliers
- Re-coding and converting variables when it was appropriate
- Re-run of frequency distribution checks for recoded variables.

Before the process of data analysis began, checks were made to ensure that the appropriate tests were used for analysis to minimise error (view decision making table on the appropriate Statistical Test in appendix).

2.2.14 Statistical Methods and Data Analysis

Before the onset of data analysis, validity checks were done to minimise errors. The use of parametric tests in the analysis was based on the following assumptions:

- Normality: Data had a normal distribution (or at least is symmetric), or drawn from a population with normal distribution on the explanatory variable.
- Interval or ratio scale of measurement
- There was a random selection of the members of the cohort from a defined population.
- Homogeneity of variances: Data from multiple groups have the same variance.
- Linearity: Data have a linear relationship.
- Independence: Data are independent.

A model assumption for parametric tests was to ensure that a test of normality was done employing the use of the Kolmogorov-Smirnov test (> 100 participants). The test required that if the p-value ≥ 0.05, then the explanatory variable under consideration was normally distributed. Alternatively, if the p-value was <0.05, then the assumptions for normal distribution had failed, leading to the consideration of non-parametric tests for analysis. When conditions of normality were violated then consideration favoured the used of median and interquartile (IQR) ranges (a measure of variability) as appropriate measures of comparison for continuous variables. In normality-distributed conditions, the mean, and standard deviation were appropriate for continuous variables.

Model assumptions for parametric tests at the level of interval data also required that data meet the requirement of homogeneity of variance. This was computed by using the Levene's test; if the p-value was < 0.05, this assumption was violated.

The unpaired t-test was used to explore differences between two independent variables that had a normal distribution pattern, the Mann Whitney 'U' test was used to ascertain differences between the comparison groups when they were at an ordinal level of data. The Chi-squared (X^2) test was used as a test for difference in nominal or categorical variables of independent groups. For the Chi-squared test, significantly observed associations was at p-value <0.05. With groups of nominal data, McNemar's test was used to ascertain any changes in the groups.

For repeated measures within matched pairs, Wilcoxon Signed ranked test was the non-parametric approach to explore any differences between the matched pair. Evaluations, when continuous data was involved, employed the use of ANOVA. Correlations to determine levels of associations between variables employed the use of Chi-squared test of association and Spearman's correlation coefficient respectively when the variables were either nominal or ordinal.

Re-coding and stratification of variables with normal distribution was done to minimise the advent of type I and type II errors. The process of re-coding and stratification applied to the following variables sex, IMD, TC, TG, LDL, HDL, SBP, DBP, TSH, and serum creatinine. Others included age at diagnosis, age at death, and duration of diagnosis.

Glycaemic control using HbA_{1c} was recoded into categories of deciles: HbA1c (%) [mmol/mol] ≤ 5.9 [≤41], 6.0-6.4[42-46], 6.5-6.9[48-52], 7.0-7.4[53-57], 7.5-8.0[58-64], 8.1-8.4[65-68], 8.5-9.0[69-75], 9.1-9.4[76-79], 9.5-10[80-86], ≥ 10.1[>87].

Classification based on socioeconomic status was via the parameter IMD, following an organization into quintiles; Quintile 1 [most deprived], Quintile 2 [above average], Quintile 3 [average], Quintile 4 [below average], Quintile 5 [least deprived]. Smoking status was initially categorised based on the following responses; non-smokers, smokers, ex-smokers and never asked and then realigned into the categories never smoked, smokes and ex-smokers. Classification of weight was aligned into the following classification; BMI [kg/m2] Underweight [< 18.5], Normal range [18.5 -24.99], Overweight [≥ 25.00], Pre-obese [25.00 – 29.99], Obese class I [30.00 – 34.99], Obese class II [35.00 – 39.99], Obese class III, [≥ 40]. Values for serum creatinine (µmol/l) were categorised into quintiles of < 61, 62-106, 107-129, 130-149, and ≥ 150. For ease of analysis 3 of these categories were important 107-129 µmol/l corresponding to (GFR 45-89ml/min/1.73m^2 or mild or stage 2 CKD), 130-149 µmol/l corresponding to (GFR 30-45ml/min/1.73m2 or moderate or stage 3 CKD) and ≥ 150 µmol/l corresponding to (GFR < 30ml/min/1.73m2 or severe or stage 4 and 5 CKD). Systolic blood pressure (mmHg) were categorised into quintiles of ≤ 99, 100–119, 120–139, 140–159, and ≥160. Diastolic blood pressure (mmHg) were categorised into sextiles of ≤ 59, 60-69, 70 – 79, 80 – 89, 90- 99, and ≥100.

In considering the lipid profiles, values for total Cholesterol [TC] (mmol/L) were initially categorised as desirable ≤ 5.18, borderline high 5.18 - 6.18 and high ≥ 6.22 but transformed into quintiles in the following order; ≤ 3.9, 4.0-4.5, 4.6-5.2, 5.3-6.1, and ≥6.2. The values

obtained for total triglycerides [TG] (mmol/L), had initial classifications of desirable ≤ 1.70, borderline high 1.7 - 2.2, high 2.3- 5.6, and very high ≥ 5.6 but re-classified into tertiles of ≤ 1.6, 1.7-2.2, ≥ 2.3 to allow for ease of comparison. The values for LDL (mmol/L) had a classification into quintiles of optimal ≤ 2.59, near optimal, 2.59 - 3.34, borderline high 3.37 - 4.1, high 4.15 - 4.90, and very high ≥ 4.90. HDL (mmol/L) was classified into quartiles of 0.4-0.7, 0.8-1.1, 1.2-1.5, and ≥ 1.6. TC/HDL ratio was organised into tertiles of ≤ 3.5, 3.6-5.0, and ≥ 5.1, and LDL: HDL ratio into tertiles of ≤ 1.5, 1.6-3.6, and ≥ 3.7.

The classification of the age of diagnosis, the age of death or censored was categorised into 17 age groups 0 – 4, 5 – 9, 10 – 14, 15 – 19, 20 – 24, 25 – 29, 30 – 34, and 35 – 39. Adjustments were made to account for the variability of effect sizes according to age and sex using the standard population of the Wirral peninsula obtained from mid-year population estimates for the study period.

In ascertaining event history analysis, it was essential to establish a follow-up period for the study. This period was set from the 1st of January 2000 to the 31st of December 2012. This period coincided with the period when the database was quality appraised and the beginning of the close of the register. Due to the variability at which participants entered into the study, it was essential to establish person-time for the study. This was done to establish the actual time for which every participant in the study was at risk (in years). This allowed for the estimation of incidence rates, prevalence rates, relative risk, and absolute risk. The prevalence rate was the statistical estimation of the number of participants with T1D at a particular given time. The incidence rate was an estimation of the number of new cases or diagnosis made within a specified period. The incidence and prevalence rates allowed for the computation of the relative risk defined as the comparison of the probability of a health event occurring in an exposed group (T1D population) as compared to the control group in a given period. In the analysis of mortality in this population subset, an estimate for the absolute excess risk was computed, this variable determines the difference between the observed mortality and expected mortality in the exposed and control groups divided by the person-years at risk. Standardised mortality ratios (SMR), provided computed estimates of the ratios of mortality observed in the study population as compared to the expected number of deaths while considering the age and sex-specific rate of standard populations and their 95% confidence intervals (95% CI). Computation of the SMRs utilised the formula below;

$$SMR = (observed\ deaths\ in\ each\ age\ group\ in\ T1D) \times 100\ expected\ deaths \div (Age\ specific\ mortality\ rate)(total\ population\ in\ T1D\ in\ each\ age\ group)$$

Values for relative mortality and excess mortality were also estimated. The relative mortality was an estimate of the division of the observed mortality by the expected mortality while the excess mortality was the observed difference between the observed mortality and expected mortality (Elie et al. 2011; Lau, Cole, & Gange, 2009). Estimates for the age-specific, age-adjusted and sex-specific mortality rates were computed. The age-specific mortality rate is an estimate of the total number of deaths for each age group per 1000 populations in a given year. The estimations of age-specific, age-adjusted and sex-specific mortality rates allowed for mitigating the influence of age and sex in this cohort, it also allowed for overall comparisons to the national estimates.

A complex algorithm was designed using Cox regression with left-truncation used to provide reliable estimates of competing risks as stratifying factors; this method allowed for computation of survival analysis using the Kaplan-Meier method. The Cox regression model was also used to allow for the computation of hazard ratios of mortality. In sub-group analyses of repeated measures, multiple linear regressions analysis considered the variables of HbA_{1c}, SBP, and DBP as dependent variables, while the variables of age, sex, smoking duration of T1D, BMI, and socioeconomic status were considered as independent variables. The Cox proportional hazard model made provisions for the analysis of risk factors as continuous covariates. Log cumulative hazard plots were obtained using the assumptions of the proportional hazard model, for all variables of the competing risk. The covariates for the Cox proportional model were gender, systolic BP (mmHg), diastolic BP (mmHg), smoking status, serum creatinine (µmol/l), HbA1c (%), BMI (kg/m2), IMD quintiles, total cholesterol (mmol/l), high-density lipoproteins (mmol/l), low-density lipoproteins (mmol/l), triglycerides (mmol/l), TC/HDL ratio, LDL/HDL ratio, age at diagnosis, and duration of diagnosis. Adjustments were made to determine which variables were significant and on which the Cox model was dependent. Computation of within subgroup sensitivity analysis ensured a determination of specific subgroups that contributed to the hazards ratios obtained.

The register and supporting information from available case notes allowed for the computation and analysis of large amounts of data; however, this study focussed on the following areas for analysis:

- Glycemic levels and mortality
- All-cause mortality
- Biochemical parameters and mortality
- Socioeconomic status and mortality
- Life expectancy
- Analysis of microvascular complications in which retinopathy was used as a proxy

The analysis of life expectancy of the participants in this study utilised the abridged model extrapolated using SPSS, following principles set out by Reed & Merrell (1997). This method utilised an age-specific mortality rate for specific age bands. However, there was a potential for skewed observations because of the relatively small sample sizes and small numbers of observed death.

Additionally, Years of Potential Life Lost (YPLL) were also calculated. This is a measure of premature mortality for each participant that died during the study period. This allowed comparative analysis of excess mortality in T1D study participants were compared to the standard population. Median survival, defined as a statistical measure of survival for study participants, was also computed.

The objectives of this study were:

- To evaluate factors relating to all-cause mortality, cardiovascular and non-cardiovascular mortality
- To examine the role of variables such as socioeconomic status, smoking status, body mass index, blood pressure measurements, glycaemic control, lipid profile, nephropathy, and retinopathy as predictive risks of mortality
- To evaluate the influence of age at diagnosis, duration of diabetes, year of diagnosis and gender on mortality.
- To evaluate life expectancy and mortality patterns in T1D

In summary, this chapter provides an overview of the conduct of this research. The next chapter is a systematic review that explores current global evidence on trends in mortality risk for T1D relative to the general population, including all-cause, cardiovascular and non-cardiovascular mortality.

Chapter 3: A Systematic Review and Meta-Analysis of All-Cause and Cause-Specific Mortality in Type I Diabetes Mellitus Including Gender Specific Risk and Time-Based Trends

3.1 Introduction

This chapter is a systematic review designed to review the research objective of establishing what the current evidence on trends in mortality risk is for T1D relative to the general population, including all-cause, cardiovascular and non-cardiovascular mortality. The diagnosis of T1D confers the risk of developing both micro- and macro-vascular complications which can be either acute or chronic. These complications contribute to the mortality index of T1D (IDF, 2013) with studies revealing mortality rates as high as 42.6 deaths per 100,000 children in countries such as Sudan, and as low as 0.63 deaths per 100, 000 children in the USA (IDF, 2013). In the lower age groups (15- 34 years), there is increased risk of mortality of almost 3 times that of the general population which is attributed to acute metabolic complications. Diabetic ketoacidosis (DKA) is reported to account for 20% of deaths and hypoglycaemia is reported to account for almost 4% of deaths. For those in the older age groups

(above 30 years), mortality is primarily due to chronic complications including cardiovascular disease (CVD) which accounts for 10 times higher risk compared to the general population (National Diabetes Audit, 2011). One study reported that CVD accounts for the highest cause of death in T1D at 44% of all deaths, and diabetic nephropathy accounted for 21% of all-cause mortality.

Some studies have proffered that T1D confers an increased relative risk of mortality as compared to the general population; however, there have been very few systematic reviews to attest to this finding. Only one study Lung et al. (2014) suggested an increased relative risk of mortality in T1D as compared to the general population with significant heterogeneity across studies included. However, there is a lack of research in ascertaining what the relative risk of mortality is in cause-specific complications of the T1D as compared to the general population.

Another trend is the gender-specific mortality difference that T1D confers. Studies reveal that women with T1D possess an increased risk of mortality that could be as high as 9 times that of the general population, although this trend varied across studies (Dahlquist, and Källén, 2005; Soedamah-Muthu et al. 2006) but a systematic review showed an increased risk of premature mortality in women (Huxley, Peters, Gita, & Woodward, 2015).

Management modalities in T1D have also witnessed significant improvements in the last 2 decades such as the availability and use of insulin pumps, continuous glucose monitoring (CGM), use of statins to protect against atherogenic risk factors, and use of ace inhibitors for renal and cardiac protection. However, despite these advancements in treatment, there has been only marginal improvements in life expectancy with a 2014 Diabetes UK report showing that those with T1D can expect a reduced life expectancy of almost 20 years (Diabetes UK, 2014) as compared to 27 years in the 1970s (Goodkin, 1975). Some variations have been reported by various studies between 11 and 13 years by Livingstone et al. (2015) 16.5 years in the 1980s by Brown, Scott, & Moir, (2001), and 4 years by Miller et al., (2012).

In summary, there is a lack of research to show what the relative risk of mortality is in cause-specific complications of the T1D relative to the general population, the current discrepancy with variations in gender-specific mortality risk, and variations in life expectancy despite improvements in management modalities. The purpose of this study is to complete a systematic review and meta-analysis to establish all cause and cause-specific mortality as it relates to those with T1D, including gender-specific risk and time-based trends associated with the condition.

3.2 Methods

Aim: Is to conduct a systematic review and meta-analysis, in order to present current evidence of all-cause and cause-specific mortality amongst T1D patients.

Objectives

- To assess all-cause mortality in T1D as compared to the general population.
- To assess cause-specific mortality in T1D as compared to the general population.
- To compute any gender variations in cause-specific mortality associated with T1D
- To explore subgroup meta-analysis in showing time-based trends inT1D.

3.2.1 Inclusion criteria for studies

Studies were included if they meet the following methodological criteria;

- Existing systematic reviews
- Randomised Controlled Trials
- Cohort studies
- Epidemiological studies

Population/types of participants and characteristics

Studies included had participants diagnosed with Type 1 Diabetes before the age of 40 years, as it becomes progressively challenging to differentiate between type 1 and type 2 diabetes. Included also were individuals receiving insulin therapy within the first year of diagnosis, physician-diagnosed type 1 diabetes at enrolment.

Comparator: The studies included had a comparison population that was either a comparison cohort or general population.

Outcome measures*:* The outcome measures used were standardised mortality ratio (SMR) a form of relative risk (RR). Primary outcome of this study was. Overall mortality rates/all-cause mortality. Secondary outcomes for this study were;

1. Gender and mortality risk
2. Year of study baseline
3. Follow-up duration
4. Cause-specific mortality (overall and according to gender)

a) Cardiovascular disease (inclusive of coronary artery disease, myocardial infarction, heart failure/disease, ischemic heart disease)
b) Cerebrovascular disease (stroke)
c) Renal disease
d) Cancer
e) Accidents and suicide

3.2.2 Exclusion criteria for studies

Studies that did not explicitly meet the inclusion criteria were not included, any study that had a CASP score (Quality appraisal) less than 8 were excluded, other reasons for exclusion of studies were any studies whose participant acquired type 1 diabetes from a secondary cause; those that only had abstract without being able to access the full paper; studies that had diabetes alone without any differentiation between type 1 and type 2 diabetes; studies that never had any comparison population (either cohort or general population) and studies without adequate data for analysis were excluded.

3.2.3 Search strategy

A systematic, detailed search was conducted on both published and unpublished data that were eligible to meet the inclusion criteria. Databases were searched using MeSH terms and Boolean keyword phrases. An initial search was done covering electronic databases PubMed, Medline, Campbell Library of systematic reviews, Cochrane database of systematic reviews (CDSR), EMBASE and PAIS international, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, World Health Organisation Library and Information Network for knowledge database (WHOLIS), The Centre for Evidenced-Based Medicine, PsycINFO, National Library for Health, Ongoing Reviews database, British Nursing Index and SCOPUS (Higgins & Green, 2011).

The search was extended to unpublished data such as the UK National Research Register (NRR), ReFeR, Kings Fund and Conference Papers Index. FADE, ProQuest Dissertation and mTheses, and other Indexed Citations up to 2015, National Technical Information Service (NTIS) and Health Management Information Service. Finally, a manual search of reference list of some studies was done to identify any potential studies that meet the inclusion criteria.

Studies included were written in the English language. Search period used was between January 1960 and March 2016 to provide an overview of trends about more recent evidence. It is also the period where significant changes in the management of T1D were instituted.

3.2.4 Search Terms

Keywords and phrases, including Medical Subject Headings (MeSH), will include; ‘‘Type 1 diabetes mellitus mortality’’, “Type 1 diabetes mortality”, ‘‘mortality and type 1 diabetes’’, ‘‘excess mortality and type 1 diabetes’’, ‘‘mortality rates and type 1 diabetes’’, “Type I diabetes and mortality”, “Type 1 DM and mortality”, “Type 1 DM and mortality”, “determinants of mortality and type 1 diabetes”, ‘‘mortality predictors and diabetes’’.

3.2.5 Data extraction and synthesis

Data extracted from the studies were as follows; 1st Author (year of publication), Title and Design of study, Setting (year of Study), Study size [number deceased], Comparison population, Participants Characteristics (age range, male-female distribution), Definition of incident cases, Duration and follow up period and Outcome Measures. See table 1 in the results section

3.2.6 Quality appraisal

To ensure a transparent, rigorous process, quality appraisal was done using the Critical Appraisal Skills Programme (CASP) tool. A quality score was calculated for each of the included studies by AE, and these scores were verified and triangulated by HC and DBJ. Any discrepancies were discussed within the team to ensure transparency. (see appendix)

3.2.7 Statistical analysis

The software Review Manager (version 5.3) was used for statistical analysis, for the outcome all-cause mortality, the inverse variance method was applied using the random effect model to estimate the risk ratios (RR). The estimations of risk ratios (RR) involved calculating the log [SMR] and standard errors (SE), back-transformed to estimate the risk ratios (RR) at 95% confidence limit. The I-squared (I^2) estimates were accessed to test for heterogeneity across studies. Other outcomes that employed the inverse variance method but used the fixed effect model of analysis were cardiovascular risk with T1D; renal mortality risk with T1D; and neoplasms mortality risk with T1D; likewise, subgroup analysis such as year of study published and follow-up duration employed the inverse variance method using the fixed effect model of

analysis. The outcomes of gender-specific mortality made use of dichotomous data employing the Mantel-Haenszel statistical method, using the random effect analysis model to estimate the average effect estimate of the measure risk ratio. The outcomes cardiovascular mortality risk according to gender also employed a similar method. The outcomes renal mortality risk according to gender, neoplasms mortality risk according to gender, cerebrovascular mortality risk according to gender, and accidents and suicides mortality risk according to gender employed the Mantel-Haenszel statistical method using dichotomous data but used the fixed effect model analysis. The decision to make use of either the random or fixed model of analysis was predicated on information retrieved from a book on meta-analysis written by Borenstein and colleagues in (2009).

3.3 Systematic review results

The result section will elaborate details on search results, study selection process, an overview of included studies, quality appraisal and meta-analysis.

3.3.1 Search Results

Table 3.1 shows a summary of the search process of accessing the databases. The study selection process involved a liberal search of electronic databases. This yielded a total of 10,572 articles with subject heading related to T1D, after removal of duplicates (160) we were left with 10,412 articles, with the application of the inclusion criteria (at abstract level), 238 articles were obtained, a full-text review of these 238 articles showed that 35 articles meet the inclusion criteria and these articles were used for qualitative and quantitative data synthesis (Figure 3.1). Following retrieval of these 35 studies, quality appraisal using the CASP tool (appendix VI) and full descriptive synthesis was done (table 3.3).

Table 3.1: Initial study search process

Database Search	**Search terms (Keywords)**	**Date assessed (2015)**	**Number of studies identified with the liberal screening of database**	**Excluded due non-relevance to inclusion criteria and research question.**	**Studies for more detailed evaluation**	**Limit to the number of years and language restrictions (January 1960 to December 201)**
CINAHL Plus with full text	"Type 1 diabetes mellitus mortality.''	1/03/16	1667	1607	60	Limit to 55 years, no language restrictions.
PubMed Central	"Type 1 diabetes mellitus mortality.''	1/03/16	4679	4642	37	Limit to 55 years, no language restrictions.

PubMed	"Type 1 diabetes mellitus mortality.''	1/03/16	3011	2876	135	Limit to 55 years, no language restrictions.
Cochrane Library	"Type 1 diabetes mellitus mortality.''	1/03/16	554	552	2	Limit to 55 years, no language restrictions.
WHOLIS	"Type 1 diabetes mellitus mortality''	1/03/16	3	0	0	Limit to 55 years, no language restrictions.
ProQuest	"Type 1 diabetes mellitus mortality.''	1/03/16	592	588	4	Limit to 55 years, no language restrictions.
LILACS	"Type 1 diabetes mellitus mortality''	1/03/16	62	0	0	Limit to 55 years, no language restrictions.
CAMPBELL	"Type 1 diabetes mellitus mortality''	1/03/16	0	0	0	Limit to 55 years, no language restrictions.

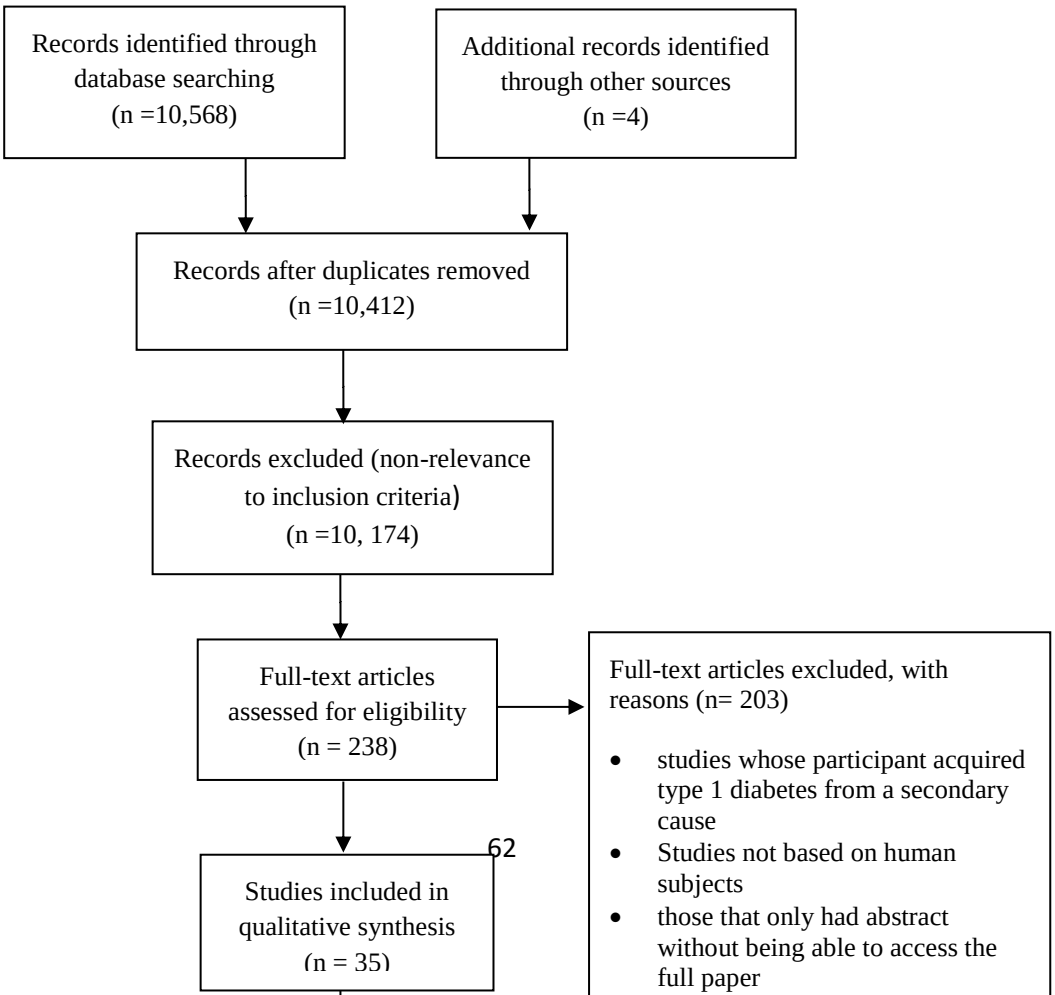


Figure 3.1: Flow diagram of the study selection process adapted from the PRISMA statement

Table 3.2: Overview of included studies and initial descriptive synthesis

S/N	1st Author (year of publication)	Title and Design of Study	Setting (year of Study)	Study size [number deceased]	Comparison population	Participants Characteristics (age range, male-female distribution); Definition of incident cases	Duration and follow up period	Outcome measures
1	Asao et al. 2003	Retrospective cohort study	Japan and Finland (1994 to 2003)	6516 overall (1,390 Japan and 5,126 Finland); [456 overall]	With diabetes and the general population	Japan (men 566, women 842), Finland (men 2817, women 2309). Definition of cases for Japan gotten from attending doctors, residence registry, family registry, for Finnish cohort was from the National Social Insurance Institution with record linkage to the National Death Registry	16.3 ± 3.8 and 17.8 ± 4.5 patient-years (mean follow up). The study was 25 years.	All-cause mortality
2	Alleman 2009	Retrospective cohort study	Switzer-land	533 patients (225 type1, 308 type2 diabetes, 52.2% men) were followed for 30 years	With Diabetes and the general population	Protocol from the WHO Multinational Study of Vascular Disease in Diabetes	30 years	All-cause mortality, gender-specific cardiovascular and non-cardiovascular mortality
3	Barcelo 2006	Retrospective study	USA and Cuba	1391 overall (887 US and 504 Cuba); [137 overall]	With Diabetes and general population	US (men 449, women 438); Cuba (men 259, women 226).Diagnosis by a physician, daily insulin injection before the 15th birthday.	18.8 years	All-cause mortality, acute complications, nephropathy, CVD, Infections, Unknown, others
4	Bosnyak et al. 2005	Longitudinal study	USA	1261 overall	With Diabetes and general population	(men 595, women 626); participants from two Type 1 diabetes incidence registries, the Allegheny County, PA Registry and the Children's Hospital of Pittsburgh Registry		All-cause mortality, Acute complications, chronic complications, Non-diabetes related causes
5	Bruno et al. 2008	Cohort study	Italy	1210 overall [19]	No comparison	(males 688, females 522)a population-based cohort of incident cases of the type 1Diabetes Registry of the Province of Turin	15.8 years	All-cause mortality, Acute complications, chronic complications, Non-diabetes related causes

6	Burnet et al. 2007	Cohort study	USA	1238 overall [36]	With diabetes	(males 680, females 558); Childhood Diabetes Registry with a cohort of subjects diagnosed with diabetes before age 18 years	7.75 years	All-cause mortality, Acute complications, CVD, Infection, Trauma, other causes, unknown causes
7	Collado-Mesa et al. 1997	Cohort study	Cuba	504 overall [70]	With Diabetes and the general population	(males 259, females 245) Registry data of onset of IDDM subjects, onset < 15 years	17.5 years	All-cause mortality, Acute complications, CVD, Infection, Trauma, other causes, unknown causes
8	Conway 2012	Cohort study	USA	1098 adults	Compared with 49,914 without diabetes	Registry data of onset of T1D subjects, onset < 30years years	20 years	All-cause mortality, cause-specific mortality (CVD, suicide,
9	Cooper 2014	Cohort study	Australia	1309	Compared with 6451 without DM	(males 660, females 649); Western Australian Children's Diabetes Database and clinical data		All-cause mortality, cause-specific mortality (CVD, suicide,
10	Dahlquist 2005	Cohort study	Sweden		Compared with control subjects	Swedish childhood diabetes register	15 years	All-cause mortality, cause-specific mortality (CVD, suicide,
11	Dawson 2008	Cohort study	New Zealand	995 overall subjects	Compared with the general population	(261 females, 264 males); Canterbury Diabetes Registry	20 years	All-cause mortality
12	Edge 1999	Retrospective study	UK	128 subjects overall	Compared with the general population	The Office of National Statistics (ONS) and General Register Office for Scotland		All-cause mortality, cause specific mortality (acute complications, cerebral edema).
13	Florkowski 2002	Prospective cohort study	New Zealand	995	Compared with Type 2 DM and the general population.	(502 females and 493 males); The Canterbury Diabetes Registry	15 years	All-cause and cause-specific death rates (Cardiovascular disease, Renal failure, Respiratory disease, malignancy).
14	Harjutsalo2011	Cohort study	Finland	17 306type 1 diabetes	Compared with and the	Drug reimbursement register	21.4 years	All-cause mortality, cause-specific

					general population			mortality (cardiovascular disease, renal failure).
15	Laing 1998	Cohort study	United Kingdom	23 752 diabetic patients	No comparison	Male to female ratio (62%: 38%); data from various register and GP clinics	30 years	All-cause mortality
16	Laing(a) 2003	Cohort study	United Kingdom	23 751 diabetic patients	No comparison	Male to female ratio (62%: 38%); data National Health Service Central Registers for patients from England, Wales	28 years	Cerebrovascular mortality
17	Laing(b) 2003	Cohort study	United Kingdom	23 752 diabetic patients	No comparison	Male to female ratio (62%: 63%); data National Health Service Central Registers for patients from England, Wales	28 years	Cardiovascular disease mortality
18	Laron-Kenet 2001	Cohort study	Israel	A whole-country cohort of 1861 children with Type 1 DM	General population	Male to female ratio (49%: 51%); data from Israel registry of Type 1 childhood diabetes	31 years	All-cause mortality, cause-specific mortality.
19	Lin 2014	Retrospective Cohort study	Taiwan	7,225 incident cases of Type 1Diabetes	No comparison	Male and female T1D was 3,471 (48%) and 3,754 (52%); data from National Health Insurance Service	10 years	All-cause mortality
20	Lind 2014	Registry-based observational study	Sweden	33,915 patients with type 1 diabetes	Controls	Total number (N = 33,915), females (N = 15,302)	13 years	Cause specific mortality (cardiovascular disease, cerebrovascular disease).
21	Moss et al. 1991	Cohort study	USA	1200 patients with type 1 diabetes	General population	Diabetic persons were identified by a review of the records of 452 of the 457 physicians providing primary care to diabetic persons in the year beginning July 1, 1979.	10 years	All-cause mortality and cause-specific mortality.
22	Morimoto 2013	Cohort study	Japan	A total of 1,385 patients with a diagnosis	General population	Data were retrieved from two nationwide surveys conducted on childhood-onset diabetes in 1970 and 1981.	40 years	All-cause mortality and cause-specific mortality.

				of type 1 diabetes at age <18 years				
23	Nishimura 2001	Cohort Study	USA	1,075 patients with type 1 diabetes	No comparison	Females 517 and 558 males	19 years minimum	All-cause mortality, sex and race-specific mortality
24	Otani 2014	Cohort Study	Japan	1054 Japanese subjects diagnosed as T1D	No comparison	Males 386 Females 668; patients registered at the Diabetes Centre of Tokyo Women's Medical University (TWMU)	20 years	All-cause mortality, cause-specific mortality (Acute diabetic complication, cardiovascular disease, Infections, cancers, suicide)
25	Pambianco 2006	Cohort Study	USA	906 subjects diagnosed as T1D	General population	prospective type 1 diabetes cohort visiting children's Hospital of Pittsburgh	30 years	All-cause mortality, Cause-specific mortality (cardiovascular disease, nephropathy).
26	Patterson 2007	Population-based Cohort study	Multiple sites (EURODIAB)	28,887 children diagnosed with Type 1 Diabetes	General population	EURODIAB registers	Minimum 18 years	All-cause mortality
27	Podar 2000	Population based Cohort study	Multiple sites; Estonia, Lithuania and Finland	Estonia (n=518), Finland (n=5156), Lithuania (n= 698)	General population	childhood type 1 diabetes registers	12 years	All-cause mortality
28	Raymond 1995	Population-based retrospective Cohort study	United Kingdom	(n=4680) patients Identified	General population	Population-based mortality register and all insulin-treated diabetes mellitus cases notified to the Leicestershire diabetes register		All-cause mortality, cause-specific mortality
29	Riley 1995	Cohort study	Australia	835 patients with type 1 Diabetes	General population	Female: Male ratio (54.8% to 52.4; Tasmanian Insulin-Treated Diabetes	Minimum of 8.5 years	All-cause mortality

						Register who were resident in Tasmania and using insulin on May 1, 1984		
30	Roberts et al. 2004	Cohort study	UK	4992participants	General population	Hospital admission data	28 years	All-cause mortality
31	Schober 1997	Cohort study	Austria	1185patients with Type 1 diabetes	No comparison	Males 616, Females 569; Austrian IDDM registry	12 years	All-cause mortality, cause-specific mortality (acute complications)
32	Swerdlow 2003	Cohort study	UK	828 South Asian	Compared with 27 962 non-South Asian patients	Data from Diabetes UK cohort study	28 years	All-cause mortality, cause-specific mortality
33	Skrivarhaug 2005	Cohort study	Norway	1,906 Norwegians type 1 diabetic patient	General population	Males 1,034, Females 872; Norwegian Childhood Diabetes Registry	28 years	All-cause mortality, cause-specific mortality (Coronary Artery disease, Cardiovascular disease, Diabetic Ketoacidosis, Ischaemic Heart Disease).
34	Warner et al. 1998	Cohort study	United Kingdom	1854type 1 diabetic subjects	General population	Yorkshire Children's Diabetes Register	15 years	All-cause mortality, cause-specific mortality
35	Washington et al. 2012	Cohorts study	USA	1075 in Allegheny County	General population	USVI Childhood (<19 years old) Diabetes Registry	26 years	All-cause mortality.

Of the 35 studies selected for the review, 32 studies acquired their data from registers, 2 studies acquired data from hospital admission records (Roberts et al. 2004; Moss, Klein, & Klein, 1991) and 1 study from a survey conducted (Morimoto et al. 2013). Roberts et al. (2004) were conducted in Oxford, UK; the study considered a total number of 4992 admissions for T1D between 1968 and 1996. Moss, Klein and Klein (1991) used 2982 patients identified through clinic visits and hospital records between 1980 and 1988 in 11 counties of Southern Wisconsin, USA. Morimoto et al. (2013) identified the participant cohort from nationwide surveys conducted in 1970 and 1981, with a total of 1, 385 patients. All studies were cohort studies.

Some studies provided multiple relative risk [RR] estimate for analysis because they had more than one population group being studied (Asao et al., 2003; Harjutsalo, Forsblom, & Groop, 2011; Podar et al. 2000). Asao et al. (2003) had 2 distinct sub-populations from different countries Japan and Finland, Podar et al. (2000) 3 sub-populations Estonia, Finland and Lithuania. Barcelo, Bosnyak, and Orchard (2007) 2 subpopulations from Cuba and the USA, but Harjutsalo, Forsblom, and Groop (2011) had 2 sub-populations early and late onset cohorts. These provided relative risk (RR) estimates for meta-analysis.

The studies included spanned various geographical regions, Europe; United Kingdom (Edge, Ford-Adam, & Dunger, 1999; Laing et al., 1998, 2003a, 2003b; Raymond et al., 1995; Roberts et al., 2004; Swerdlow et al., 2003; Patterson, 2007; Warner, McKinney, Law, & Bodansky, 1998), Finland (Asao et al., 2003; Harjutsalo, Forsblom, & Groop, 2011; Patterson et al., 2007; Podar et al., 2000), Austria (Schober, Schneider, Friedl, & Unsinn, 1997; Patterson et al., 2007), Sweden (Dahlquist & K¨all´en, 2005; Patterson et al., 2007), Italy (Bruno et al., 2009), Germany (Patterson, 2007), Estonia (Podar et al., 2000), Lithuania (Podar et al., 2000; Patterson et al., 2007), Hungary (Patterson et al., 2007), Spain (Patterson et al., 2007), Bulgaria (Patterson et al., 2007), other countries included are, United States of America ([USA] Barcelo´, Bosnyak, & Orchard, 2007; Bosnyak et al., 2005; Burnet, Cooper, Drum, & Lipton, 2007; Conway, May, Signorello, & Blot, 2012; Moss, Klein, & Klein, 1991; Nishimura et al., 2001; Pambianco et al., 2006; Washington et al., 2014), Switzerland (Alleman et al., 2009), Cuba (Barcelo´, Bosnyak, & Orchard, 2007, Collado-Mesa et al., 1997), Norway (Skrivarhaug et al., 2006), Australia (Cooper, de Klerk, Jones, & Davis, 2014; Riley et al., 1995), New Zealand (Dawson, Willis, Florkowski, & Scott, 2008: Florkowski, Scott, Graham, Han, & Moir, 2002), Israel (Laron-Kenet, Shamis, Weitzman, Rosen, & Laron, 2001), Japan (Asao et

al., 2003; Morimoto et al., 2013; Otani, Yokoyama, & Uchigata, 2014), Taiwan (Lin et al., 2014).

3.3.2 All-cause mortality

Results of all-cause mortality were from 23 studies which included 27 sub-populations (observations). Figure 4.2 revealed an overall pooled average effect estimate of RR 3.73 (95% CI 3.19, 4.36) for individuals with Type 1 Diabetes compared to the general population. The I^2 estimate of 97% revealed a high level of heterogeneity within the studies compared but using exclusion sensitivity analysis; no study was found to be a major contributor to the heterogeneity observed. All 27 observations reported increased mortality risk for T1D.

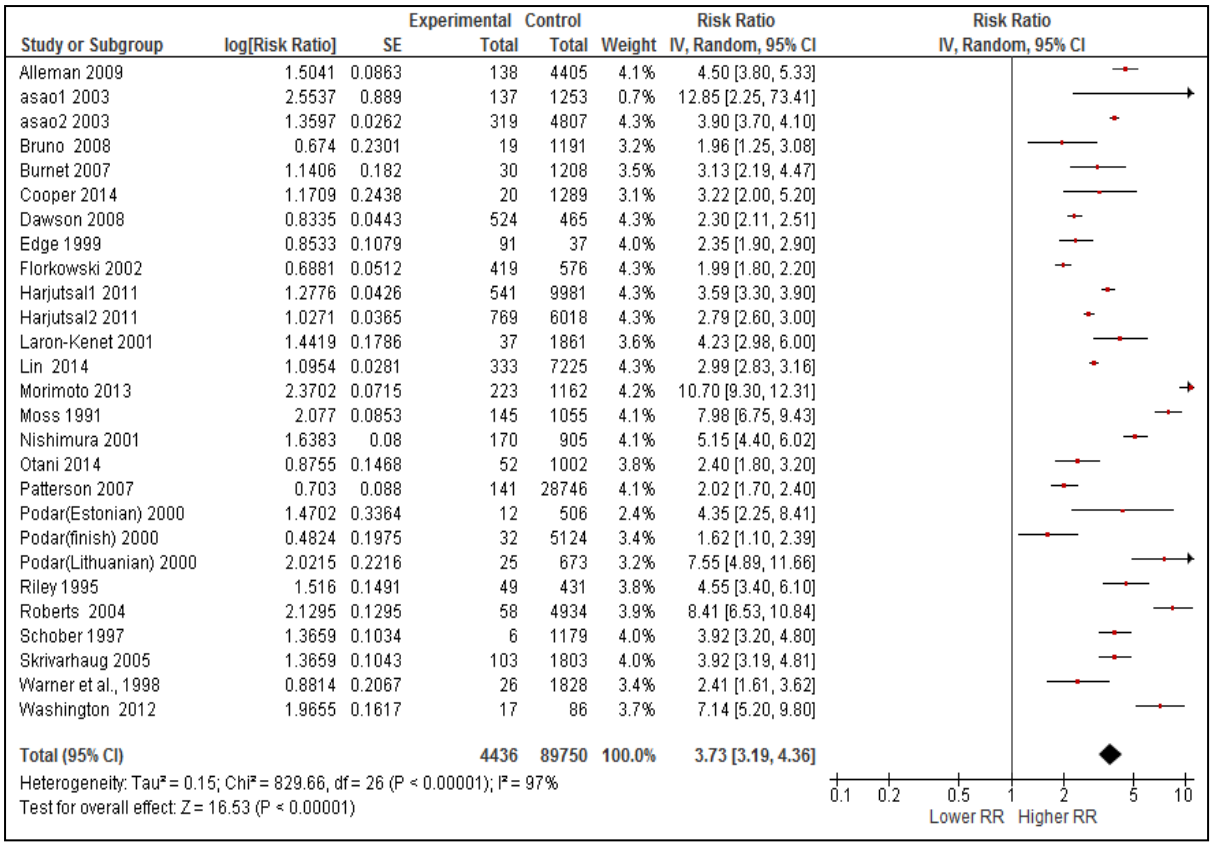


Figure 3.2: Showing forest plot of (27) studies estimating the average effect estimates for 94, 186 participants with 4436 events. The average pooled effect estimate for all-cause mortality shows higher mortality rates associated with Type 1 Diabetes

3.3.3 Gender-specific mortality

Figure 3.3 below shows mortality risk about gender, females with T1D had a higher risk of mortality compared to their male counterparts with an overall average effect estimate of RR 1.17 (95% CI 1.06, 1.29). However, 7 studies showed increased mortality risk in males relative

to females. Although this analysis of studies reports a moderate level of heterogeneity (46%), 2 studies Laron-Kernet et al. (2001) and Skrivarhaug et al. (2005) made a significant contribution to this level of heterogeneity after exclusion sensitivity analysis plot, this was as a result of factors such as methodological and clinical diversity in participant characteristics (Higgins, 2003).

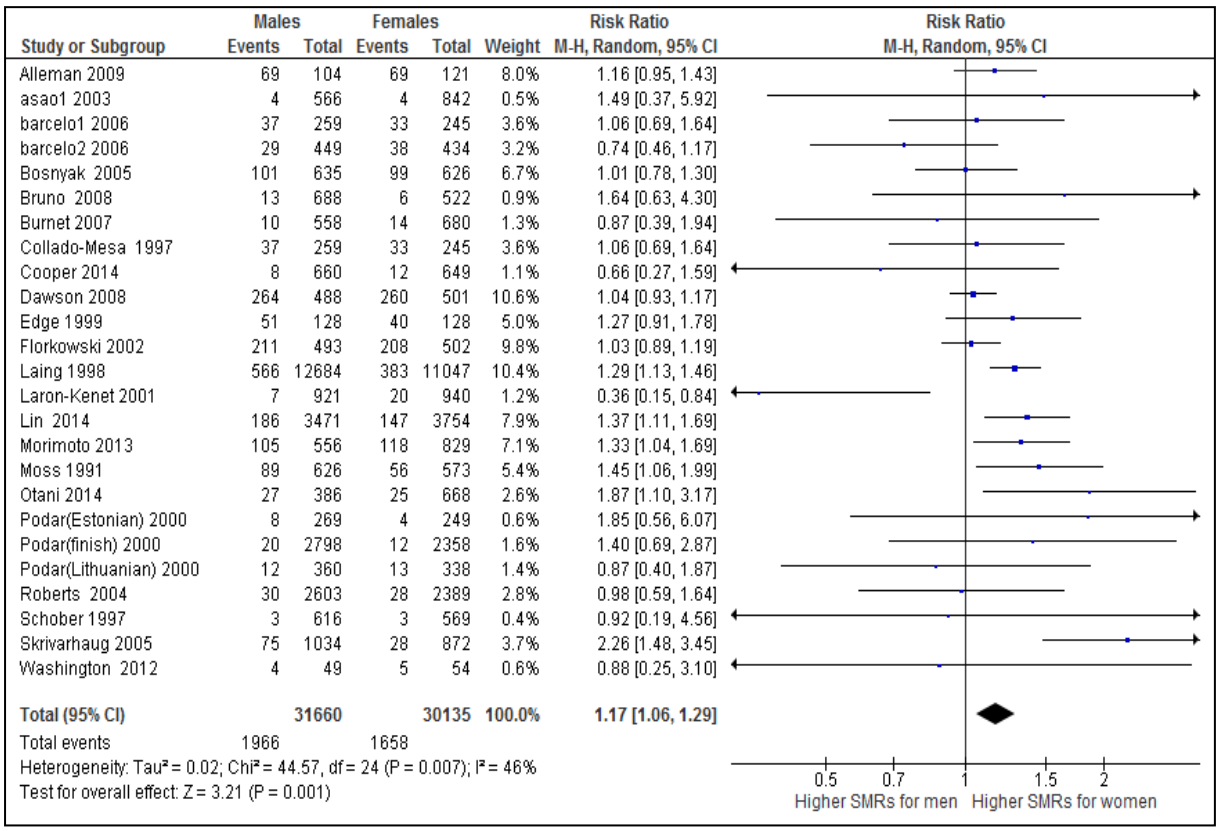


Figure 3.3: Showing forest plot of (25) studies estimating the average effect estimates for 61795 participants with total events of 3624 events. The average pooled effect estimate suggest higher risk ratio of Type 1 Diabetes mortality for women as compared to men.

3.3.4 Cardiovascular mortality risk

Figure 3.4 below shows that individuals with T1D and cardiovascular conditions have a pooled overall average effect estimate of RR 3.48 (95% CI 3.14, 3.86) when compared to the general population. This indicates that anyone who has T1D and a cardiovascular condition is at almost 200% increased risk of mortality when compared to the general population.

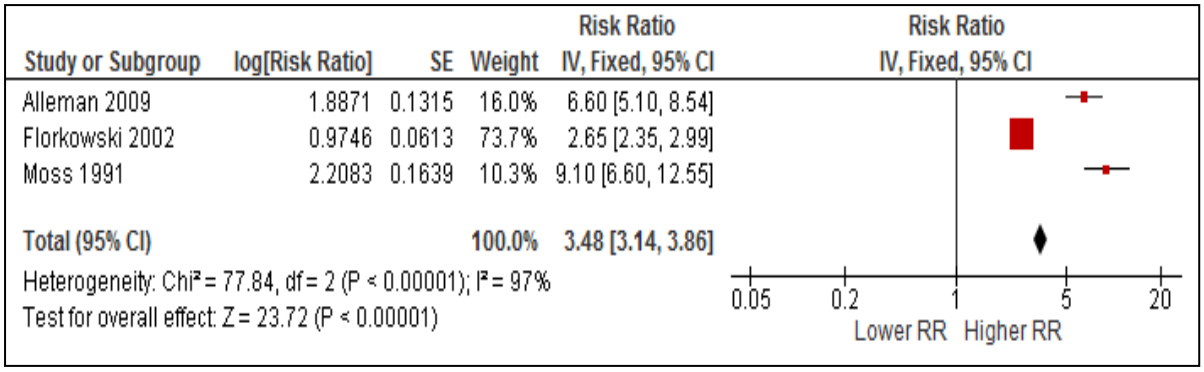


Figure 3.4: Showing forest plot of (3) studies estimating the average effect estimates cardiovascular mortality risk with type 1 diabetes. The average pooled effect estimate suggest higher risk ratio of cardiovascular mortality with type 1 diabetes compared to the general population.

3.3.5 Cardiovascular mortality risk according to gender

By comparison, females with T1D and CVD had a higher risk of mortality compared to their male counterparts with an overall average effect estimate of RR 1.41 (95% CI 0.92, 2.17). Out of the 12 studies that analysed cardiovascular mortality risk and T1D according to gender. The forest plot below (figure 3.5) showed that out of the 12 studies, 5 studies showed an increased risk of mortality from cardiovascular conditions and T1D in men while 7 studies presented an increased risk of mortality in women.

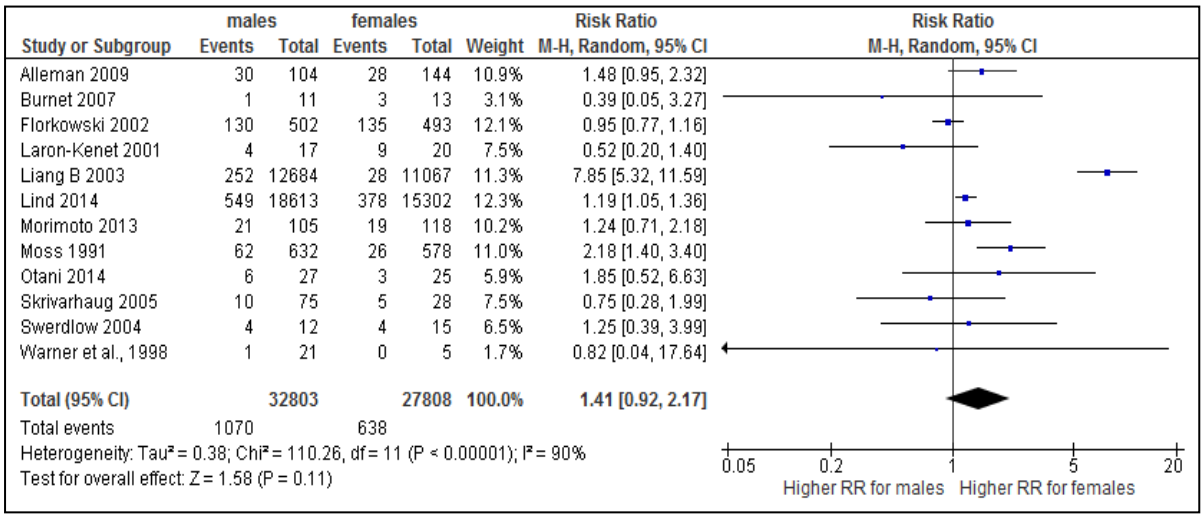


Figure 3.5: Showing forest plot of (12) studies estimating the average effect estimates for 60,611 participants with total events of 1708 events. The average pooled effect estimate suggest higher risk ratio of Type 1 Diabetes mortality for women as compared to men.

3.3.6 Renal mortality risk

Figure 3.6 below showed that individuals with T1D and renal complications had similar mortality risk compared to the general population, with an overall average effect estimate of RR 1.06 (95% CI 0.89, 1.26). However, this result should be examined with caution because of its statistical significance.

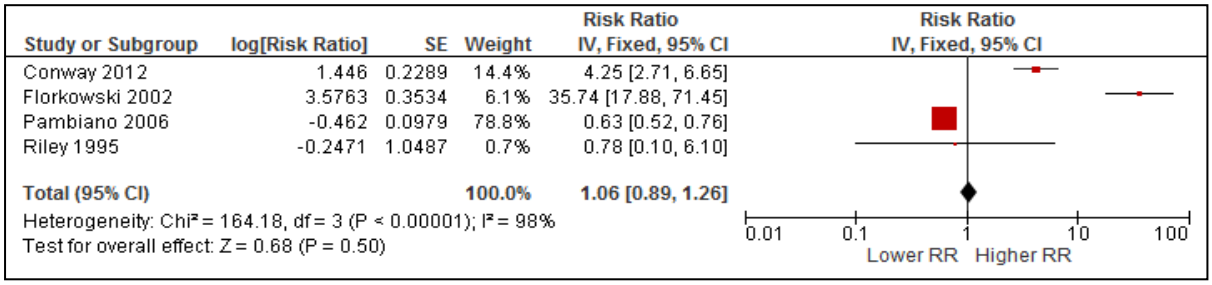


Figure 3.6: Showing forest plot of (4) studies estimating the average effect estimates. The average pooled effect estimate suggest marginally higher risk ratio of renal mortality.

3.3.7 Renal mortality risk according to gender

Figure 3.7 below shows that by comparison, males with T1D and nephropathy had a marginally higher risk of mortality compared to their female counterparts, with an overall average effect estimate of RR 0.63 (95% CI 0.38, 1.04).

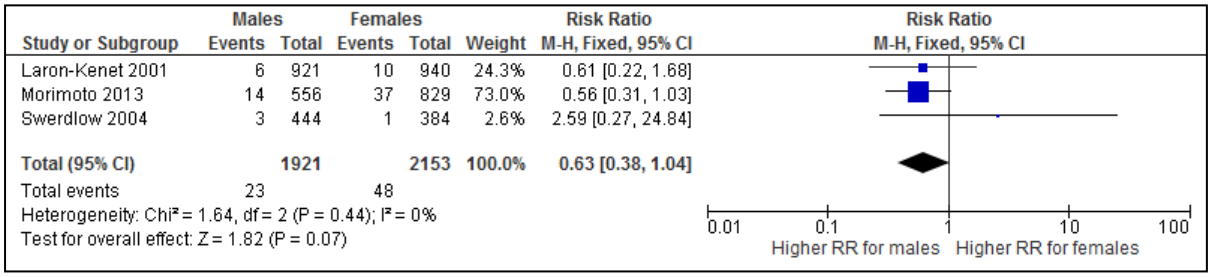


Figure 3.7: Showing forest plot of (3) studies estimating the average effect estimates for 4074 participants with total events of 71 events. The average pooled effect estimate suggest marginally higher risk ratio of Type 1 Diabetes mortality for men as compared to women

3.3.8 Mortality risk from Neoplasms

Four studies reported relative risk values for those with T1D who had any form of neoplasms carried a similar mortality risk as individuals in the general population with an overall average effect estimate of RR 1.03 (95% CI 0.92, 1.16).

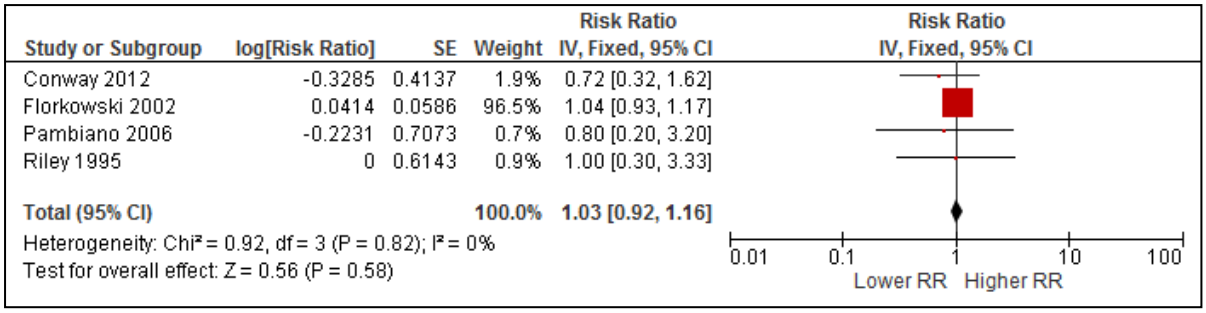


Figure 3.8: Showing forest plot of (4) studies estimating the average effect estimates. The average pooled effect estimate suggest almost equal risk ratio of mortality due to malignancy as compared to the general population.

3.3.9 Mortality risk from Neoplasms according to gender

By comparison, females with T1D and neoplasms have a marginally higher risk of mortality compared to their male counterparts, with an overall average effect estimate of RR 1.18 (95% CI 0.75, 1.86).

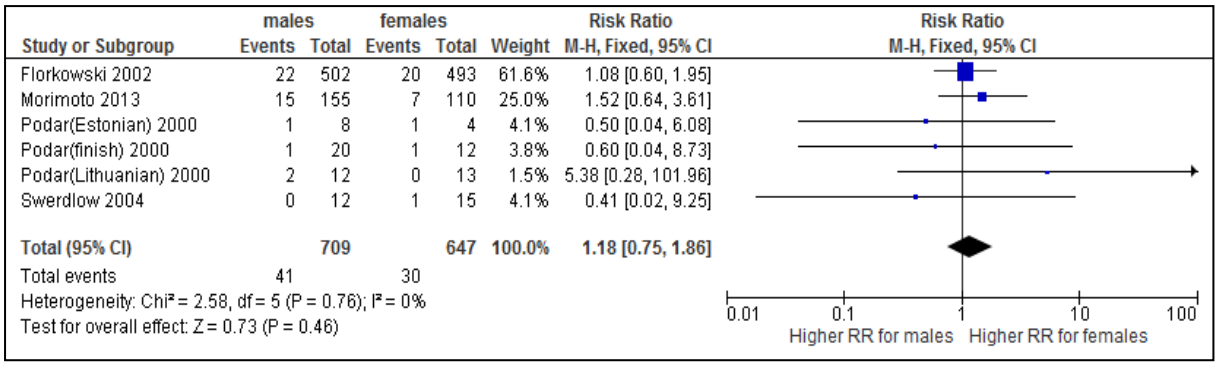


Figure 3.9: Showing forest plot of (3) studies estimating the average effect estimates for 1356 participants with total events of 71 events. The average pooled effect estimate suggests no difference in Type 1 Diabetes mortality for women as compared to men.

3.3.10 Cerebrovascular mortality risk according to gender

Figure 3.10 below showed no significant difference in cerebrovascular mortality risk between men and women with type 1 DM with an overall average effect estimate of RR 0.99 (95% CI 0.66, 1.48).

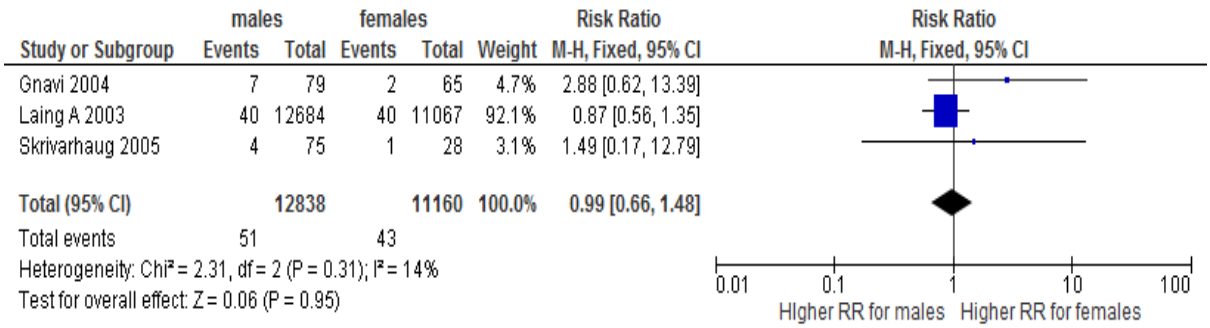


Figure 3.10: Showing forest plot of (3) studies estimating the average effect estimates for 23998 participants with total events of 94 events. The average pooled effect estimates suggest no difference in cerebrovascular mortality risk with Type 1 Diabetes with gender.

3.3.11 Accidents and Suicides mortality risk according to gender

The data showed that women with T1D are at a significantly increased risk of death from accidents and suicides compared to the men with RR 2.30 (95% CI 1.31, 4.06).

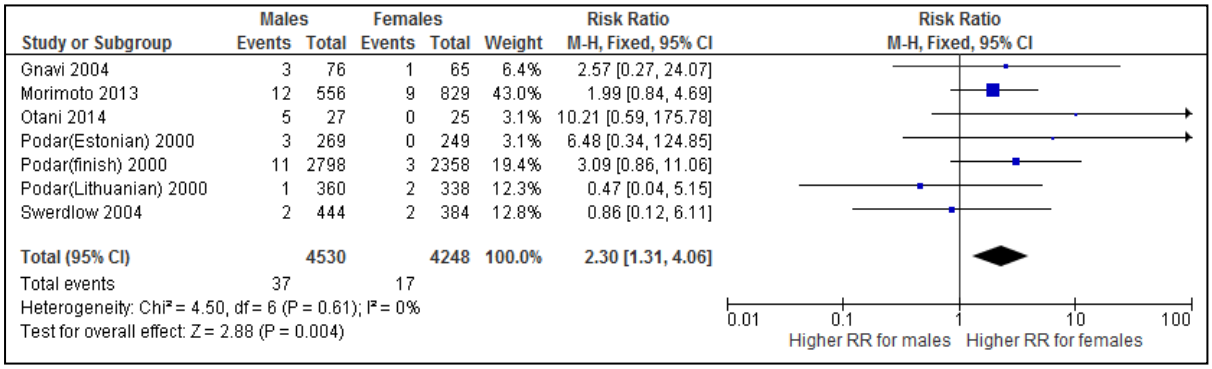


Figure 3.11: Showing forest plot of (7) studies estimating the average effect estimates for 8778 participants with total events of 54 events. The average pooled effect estimate suggests higher mortality risk in females as compared to males.

3.3.12 Subgroup analysis

An analysis of time trends was conducted using subgroup analysis according to the year of publication. Whilst findings showed significant heterogeneity among studies, Figures 3.12 to 3.14 showed temporal improvements in mortality risk over time in T1D as indicated by an overall average effect estimate of RR 4.30 (95% CI 3.92, 4.72) before the year 2000, compared to RR 3.91 (95% CI 3.75, 4.08) between the year 2000 to 2010, and RR 3.35 (95% CI 3.23, 3.47) after 2010.

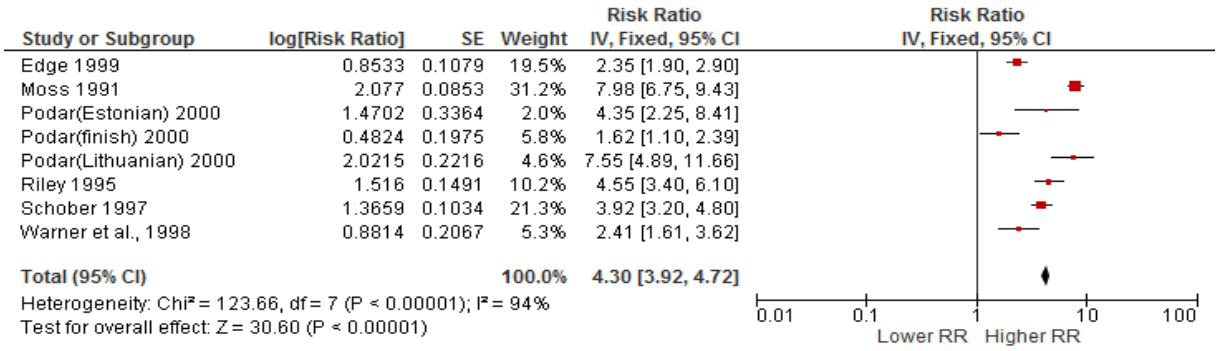


Figure 3.12: Subgroup of studies published before or on the year 2000

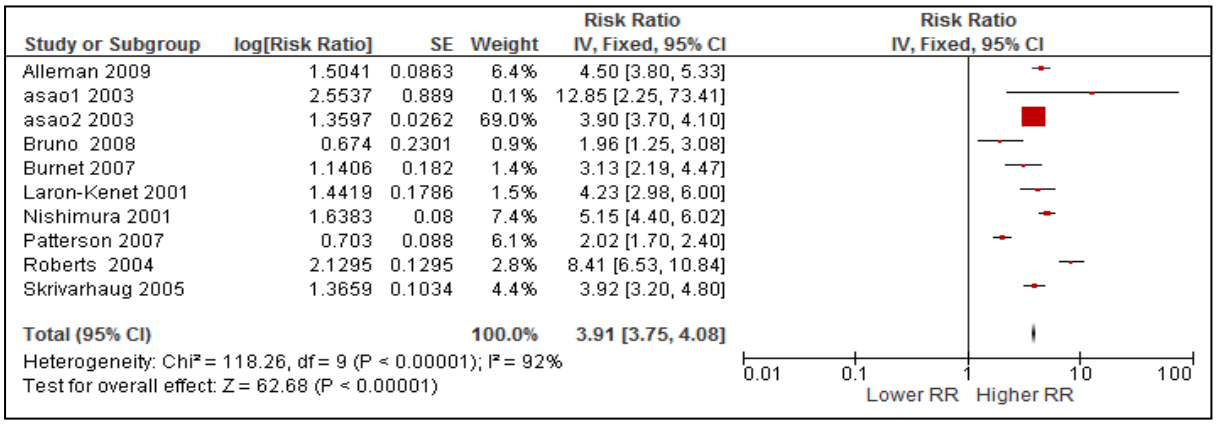


Figure 3.13: Subgroup of studies published between 2000 and 2010

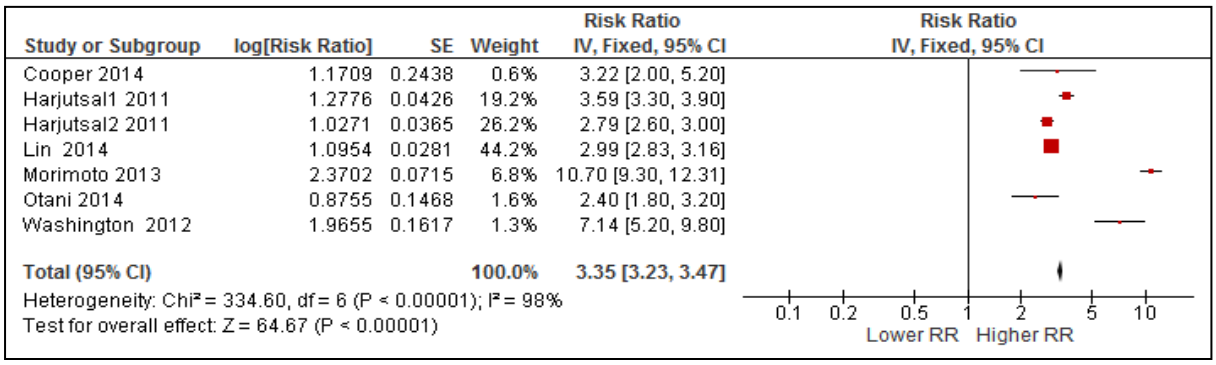


Figure 3.14: Subgroup of studies published between after year 2010

Subgroup analysis according to follow up duration

Follow up duration of patients after the diagnosis of T1D showed two peaks period in mortality. Figures 3.15 to 3.17 showed one peak period when follow up duration was less than 10 years with overall average effect estimate of RR 3.07 (95% CI 2.63, 3.58) and the other peak period when follow up duration was above 20 years with an overall average effect estimate of RR 3.50 (95% CI 3.37, 3.63).

Subgroup of studies with follow-up duration less or equal to 10 years

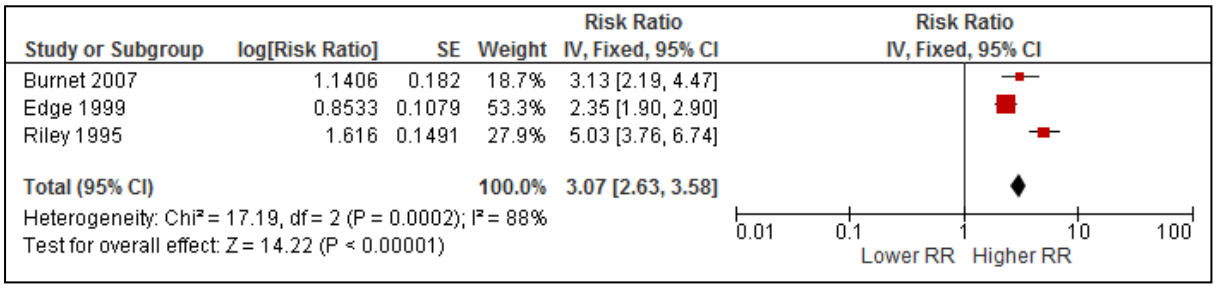


Figure 3.15: Subgroup of studies with follow up duration ≤ 10 years

Subgroup of studies with follow-up duration less or equal to 20 years

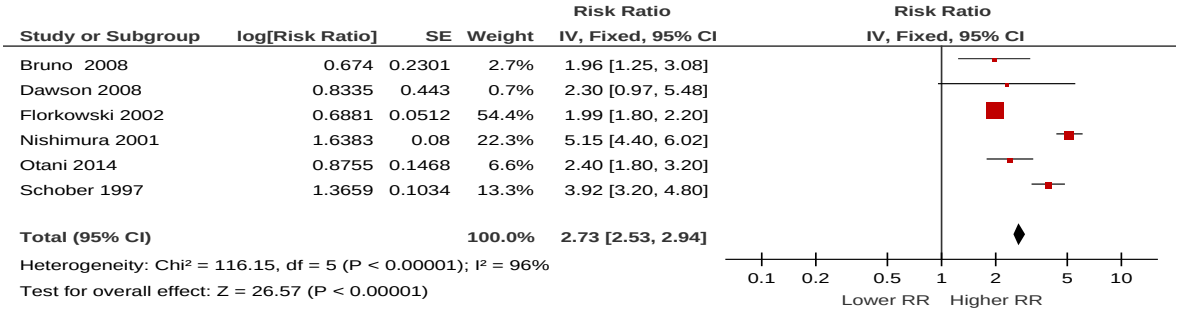


Figure 3.16: Subgroup of studies with follow up duration ≤ 20 years

Subgroup of studies with follow-up duration greater than 20 years

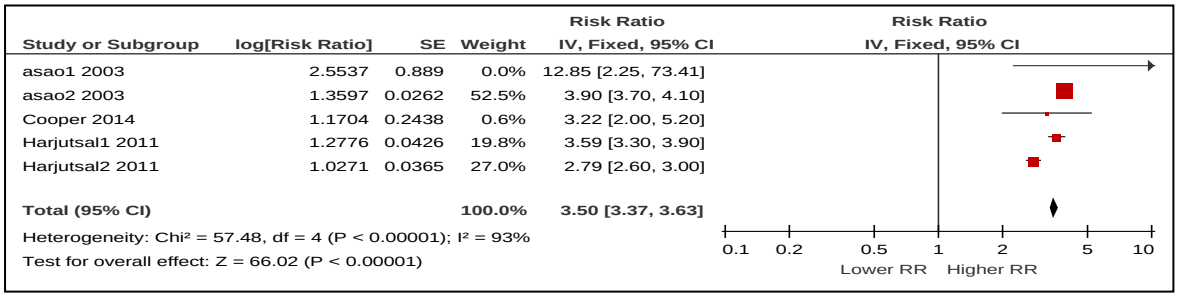


Figure 3.17: Subgroup of studies with follow up duration> 20 years

3.4 Discussion of systematic review results

This review set out to investigate the mortality risk in individuals with T1D and in so doing aimed to establish risk ratios as they relate to all-cause mortality and cause-specific mortality. Inclusive in its objectives was to establish relative risks as it relates to gender, time-based trends such as year of publication, and follow up duration. One importance of this study is its ability

to increase the precision of estimates by combining studies to yield a total population of over 90,000 participants with 4,436 deaths.

3.4.1 All-cause mortality

It is evident from this study that the diagnosis of T1D confers almost 200% increased risk of mortality (RR 3.73 [95% CI 3.19, 4.36]) when compared to the general population without the condition. This data correlates closely to findings from Lung et al. (2014). Other studies that also revealed excess all-cause mortality associated with T1D when compared to general comparative populations included Harding et al. (2014), Lind et al. (2014), Urbonaite (2002), and Gatling et al. (1997). Suggested causes for this trend include the impact of the vascular complications associated with this condition (Livingstone et al., 2012) and also, the impact of early complications in childhood and adolescence (Orchard, Costacou, Kretowski, & Nesto, 2006; Lung et al., 2014).

3.4.2 Gender-specific mortality

Regarding gender-specific associations with all-cause mortality, women were found to have a 17% increased risk of mortality when compared to their male counterparts (RR 1.17 [95% CI 1.06, 1.29]). This result confers with that of Huxley and colleagues (2015) who reported similar results (rSMR 1·37 [95% CI 1·21–1·56] p<0·0001) and also Lung et al. (2014) who reported that males had a RR of 3.25 (95% CI 2.82–3.73) as compared to females with RR of 4.54 (95% CI 3.79–5.45). Reasons behind these findings are unclear, but it has been hypothesised that women are more prone to the effects of vascular dysfunction such as the calcification of the coronary artery and dysfunction of the endothelium (Huxley, Barzi, & Woodward, 2006). Other possible reasons are that life expectancy is greater in women than in men, so women are exposed to significantly larger cumulative effects of glycaemic variations, i.e. hypo-and hyper-glycaemia (Huxley, Barzi, & Woodward, 2006). Some studies have also suggested that the physiological make up of women, such as inputs from the endocrine pathways (hypothalamus-pituitary-ovarian axis), and factors associated with puberty and menopause that affect insulin sensitivity may contribute to this gender variation (Kim, Elimi, Henderson, Cogen, & Kaplowitz, 2012; Kaplowitz, 2012; Paris et al., 2009; Amiel et al., 1986; Huxley, Peters, Mishra & Woodward, 2015).

3.4.3 Cardiovascular mortality risk

The results show that CVD in T1D carries the greatest mortality risk. Not only does it carry a significantly higher risk of mortality [RR 3.48 (95% CI 3.14, 3.86)] but this risk is over 200% greater when compared to the general population. Across all the studies included, death from CVD carried the highest risk of mortality. Other studies support this finding (Tu, Twigg, Duflou & Semsarian, 2008; Gatling, Tufail, Mukkee, Westacott & Hill, 1997; Huxley, Peters, Mishra & Woodward, 2015).

With gender, women were significantly more susceptible to CVD mortality as compared to men [RR 1.41 (95% CI 0.92, 2.17)], indicating a 40% increased risk of mortality to cardiovascular conditions as compared to their male counterparts. This result is similar to that published by Huxley and colleagues (rSMR 1·86 (95% CI 1·62–2·15) and also Gatling et al. (1997). Cardiovascular conditions were, therefore, the major cause of death in both genders, but women had significantly higher RR as compared to men. Explanations for this trend include the influence of poor glycaemic control which is more apparent in women than in men (Huxley, Peters, Mishra & Woodward, 2015; Kautzky-Willer, Harreiter, & Pacini, 2016).

3.4.4 Renal mortality risk

According to the results of this study, people with T1D have a negligible risk of mortality from renal failure compared to the general population [RR 1.06 (95% CI 0.89,1.26)]. Previous studies have suggested a reducing trend in renal mortality risk in T1D (Khalil et al., 2011; Andre´sdo´ttir et al., 2015). Explanations for this lowering trend include new management measures such as early screening for microalbuminuria, control of blood pressure, and the use of new drugs such as statins and ace-inhibitors (Khalil et al., 2011; Andre´sdo´ttir et al., 2015).

In this study, by comparison, males with T1D with nephropathy had a marginally higher risk of mortality compared to their female counterparts with an overall average effect estimate of RR 0.63 (95% CI 0.38, 1.04). This indicates an above 30% increased risk of mortality due to nephropathy in men as compared to women. However, this result contradicts the study by Huxley et al. (2015) [RR 1.44 (95% CI 1.02-2.05)] which indicated an increased risk of mortality in women compared to men.

3.4.5 Mortality risk from Neoplasm

The overall mortality risk from neoplasm in T1D is similar to that of the general population [RR 1.03 (95% CI 0.92, 1.16)], a result which correlates with that of Secrest et al (2010) but contradicts that of Hsu et al. (2014) which revealed an increased all cancer risk compared to the general population [RR 1.13 (95% CI, 1.05, 1.22)]. In relation to gender, women had almost a 20% increased risk of mortality from neoplasm as compared to men [RR 1.18; (95% CI, 0.75, 1.86)] which is similar to that reported by Hsu et al. (2014) RR 1.19 (95% CI, 1.07, 1.33), and Huxley et al (2015) RR 1.23 (95% CI, 0.79, 1.98), however in contrast to a large population study by Carstensen et al. (2016) which revealed similar Hazard Ratios in men HR 1.01 (95% CI 0.98, 1.04) and women HR 1.07 (95% CI 1.04, 1.10). Carstensen et al. (2016) also reported similar findings to this review when they analysed non-sex-specific cancers which revealed a HR 1.17 (95% CI 1.13, 1.22) among women. These results demonstrate gender as a major contributory factor in all-cause neoplasm mortality in T1D although the relationship between T1D and neoplasm is still poorly elucidated, but suggestions include hyperglycaemia as a possible link in the underlying the development of neoplasm in T1D and genetic correlations with T1D. Obesity has also been mentioned as a possible contributory link to increased risk of developing certain neoplasms in T1D (Carstensen et al., 2016).

3.4.6 Cerebrovascular mortality risk according to gender

Few studies have tried to establish an overall cerebrovascular risk as it pertains to T1D but Laing et al. (2003), in a study cohort of over 23,000 participants, reported an increased risk of cerebrovascular mortality as compared to the general population. This study was not able to evaluate this parameter due to lack of sufficient data; however, this study found a similar risk of mortality in men and women [RR 0.99 (95% CI 0.66, 1.48)]. This result should be viewed with caution because of its statistical significance p=0.95. In contrast, Huxley et al. (2015) showed an increased risk of mortality in women as compared to men.

Given that few studies have evaluated this outcome in T1D, previous studies utilised comparison with type 2 cohorts. Whilst most of them revealed an increased risk of mortality due to cerebrovascular disease in women as compared to men (Kessler, 1971; Barrett-Connor & Khaw, 1988), one study reported a comparatively similar risk in both men and women (Moss, Klein & Klein, 1991). In terms of overall cause-specific mortality as it relates to cerebrovascular risk, factors such as nephropathy, increased blood pressure and serum

cholesterol have been shown to significantly increase the risk of cerebrovascular mortality (Fuller, Stevens & Wang, 2001).

3.4.7 Accidents and Suicides mortality risk according to gender

This study highlighted that women have a significantly higher risk of mortality from accidents and suicides than men [RR2.30 (95% CI 1.31, 4.06)]. Similar results have been reported by Huxley et al. [rSMR 1.34 (0.97, 1.84)]. Some studies have revealed higher background rates of co-morbid depression in T1D the populations being studied (Grey, Whittemore, & Tam, 2002). Possible mechanisms include alcohol-related deaths, depression and drug overdose (Grey, Whittemore, & Tam, 2002).

3.4.8 Subgroup analysis

Year of publication

This study reported an overall average effect estimate of RR 4.30 (95% CI 3.92, 4.72) before year 2000, RR 3.91 (95% CI 3.75, 4.08) between the years 2000 to 2010, and RR 3.35 (95% CI 3.23, 3.47) after 2010. This indicates a mean progressive reduction in mortality risk from T1D over time, a trend also reported by Lung et al. (2014).

Follow up duration

This study found that for follow up duration of less than 10 years had overall average effect estimate of RR 3.07 (95% CI 2.63, 3.58), follow up duration between 10 and 20 years RR 2.73 (95% CI 2.73, 2.94), and follow up duration above 20 years RR 3.50 (95% CI 3.37, 3.63). These results confer with other studies, demonstrating an increased risk of mortality from acute complications in lower age groups (children and adolescents) and an increased risk of mortality from chronic complications in older age groups (Orchard, Costacou, Kretowski, & Nesto, 2006; Lung et al 2014; Huxley, Peters, Gita., & Woodward, 2015). The period between 10 and 20 years duration of follow up has been explained as a period where there is beginning to be a greater understanding of the condition and increasingly better coping mechanisms to confront the challenges of T1D (Orchard, Costacou, Kretowski, & Nesto, 2006).

3.5 Strengths and limitations

The strength of this study lies in the combination of several studies into one thereby increasing the population cohort to almost 95,000 participants and increasing the precision of estimates.

It provides both all-cause and cause-specific effect estimates for outcomes considered, giving a better understanding of mortality and T1D. Although all the studies used in the analysis were published data, provisions were made through the search strategy to include unpublished data, reducing publication bias. All languages were also considered provided translations into English were available reducing bias due to language. A potential source of bias, however, relates to the use of cohort studies. The inherent nature of their design may not fully account for all confounding variables which can affect the true estimates of the studies included.

Many of the results showed significant levels of heterogeneity. By exclusion sensitivity analysis, this study found that a few studies did contribute to this heterogeneity; but not substantially enough to account for the levels found. Major contributors were from factors such as baseline characteristics of the populations included for analysis, observed mortality trends used to estimate SMRs of the background populations, differential follow up duration of participants, participant characteristics such as differences in treatment regimens, and variations in glycaemic levels.

One limitation of this study is the use of standardized mortality ratios (SMR) as the estimates used to arrive at the risk ratios (RR) which are based on the assumption that the background population are devoid of the diagnosis of T1D.

3.6 Conclusions

In summary, this study has provided pooled overall average effect estimates for all-cause mortality, cause-specific mortality, and temporal trends for various outcomes as they relate to T1D. The study employed the use of a systematic review and meta-analysis to arrive at the results obtained. The result highlights the effects of this condition regarding survival from childhood, through adolescence and into adulthood. These results show:

1. Significant improvements in relative mortality attributed to T1D over time which can be related to improvements in treatment modalities, pharmacological and non-pharmacological interventions such as technological and lifestyle modification. This is shown in subgroup analysis where there is an increasing reduction in mortality risk over time with overall average effect estimate of RR 4.30 (95% CI 3.92, 4.72) before year 2000, compared to RR 3.91 (95% CI 3.75, 4.08) between year 2000 to 2010, and RR 3.35 (95% CI 3.23, 3.47) after 2010.

2. It also highlights the plight of females who get this condition as they are exposed more to the effects of vascular complications of T1D such as cardiovascular complications RR 3.48 (95% CI 3.14, 3.86)] and Accidents and suicides RR2.30 (95% CI 1.31, 4.06)].
3. Overall T1D carries increased mortality risk as compared to the general population (RR 3.73 [95% CI 3.19, 4.36]) with females bearing the burden of this condition (RR 1.17 [95% CI 1.06, 1.29]).

However, identified research gaps which include:

- Lack of data to fully clarify gender variations for cerebrovascular diseases, nephropathy, accidents, suicide.
- No precise data to clarify how accidents and suicides relate to depression
- no data on dementia and T1D
- coping mechanisms for patients

Chapter 4: RESULTS OF ANALYSIS OF THE DATA ON T1D IN THE WIRRAL

This chapter presents the results of analysis of the study on T1D in the Wirral. The results are presented in two overarching themes. These themes are sub-divided into two divisions below:

Division 1: Initial descriptive analysis including multiple regressions for predictors of mortality

- Summary of results
- Baseline characteristics
- Population density and age profile
- Epidemiology: prevalence and incidence
- Absolute risk: probability (risks) of mortality and Relative risk
- Predicting factors and mortality
- Total mortality
- Cause of mortality

Division 2: Mortality analysis, survival analysis, hazard ratio analysis and retinopathy assessment

- Age – and sex-specific mortality rates
- Age-sex- and calendar-year adjusted mortality rates
- Standardised mortality ratio
- Median survival time
- Hazard ratio
- Life expectancy
- Assessment of retinopathy

To establish incidence and prevalence in T1D for this cohort it was important to estimate the baseline characteristics and distribution of the population, which is found in Sections 4.1 to 4.3. Sections 4.4 and 4.5 highlight one of the findings of this study, they identify significant predictor variables for mortality in T1D. They also establish the relationship predicting risk factors and mortality in T1D, and cater to Objectives 2 and 3 of this study. This study reveal that the predicting risk factors of gender, age at diagnosis, duration of T1D, BMI, serum creatinine levels, SBP, total cholesterol, LDL, HDL, TC\HDL, and LDL\HDL showed a linear increase in mortality risk (Section 4.5). DBP followed a U-shaped relationship with relative and absolute mortality, while HbA1c levels reveal a sinusoidal pattern with the highest risk of

mortality at the levels ≤ 5.9mmol/mol (41%) (Figure 4.3.6). The significant predictors of mortality in this cohort (p-value <0.05) were the age at diagnosis, duration of diagnosis, HbA1c, SBP, DBP, and triglyceride (TG) levels (Table 4.5). Objectives 1 and 4 are addressed in Sections 4.7 to 4.13. They highlight the following findings that the significant predictors (p-value <0.05) of survival for this cohort were duration of diabetes, HbA_{1c}, Serum creatinine, BMI, and lipid levels. The main cause of death in this cohort was malignancy-related eight (8) deaths (21.6%), this was followed by cardiovascular disease and sepsis, each having six (6) deaths (16.2%) respectively. Cerebrovascular disease accounted for five (5) deaths (13.5%). Death from diabetes complications (hypoglycaemia) was recorded in one (1) patient (2.7%). Life expectancy at 40 years for females was 66.2 years as compared to males 78.3 years. There has been improved survival for T1D in this cohort, 77.185 years [95% CI: 75.191 – 79.179] in males and 76.011 years [95% CI: 73.169 – 78.000] in females.

4.1 Baseline characteristics

The numbers of participants with T1D that met the selection criteria from the Wirral Diabetes register were 1458. They were subdivided into baseline characteristics of females, males, survivors (alive) and non-survivors (dead); Table 4.1 illustrates this.

Table 4.1: Distribution of predicting variables according to total, survivors, non-survivors, and gender in T1D using Mean (years) ± SD and Median (years) ± IQR, in the Wirral.

Characteristics	Females	Males	Survivors (Alive)	Non-Survivors (Dead)	Total T1DM
Age at Diagnosis					
Mean (years) ± SD	17.49 ± 9.60	19.06 ± 10.47	17.98 ± 10.05	22.96 ± 9.82	18.37 ± 10.12
Median(years) ± IQR	15.00 ± 15.00	18.00 ± 16.00	16.00 ± 16.00	23.00 ± 15.00	17.00 ± 15.00
Age at death/Censored					
Mean (years) ± SD	42.43 ± 17.29	41.91 ± 17.54	40.72 ± 16.65	57.95 ± 17.78	42.14 ± 17.40
Median(years) ± IQR	42.00 ± 26.00	42.00 ± 25.00	41.00 ± 25.00	61.00 ± 30.00	42.00 ± 26.00
Duration of diabetes					
Mean (years) ± SD	25.21 ± 15.26	23.33 ± 15.24	22.62 ± 13.96	41.69 ± 18.44	24.15 ± 15.27
Median(years) ± IQR	23.00 ± 22.00	20.00 ± 22.00	20.00 ± 21.00	43.50 ± 28.00	21.00 ± 22.00
SBP (mmHg)					
Mean ± SD	127.78 ± 16.27	130.02 ± 14.24	127.57 ± 14.27	142.99 ± 17.47	128.98 ± 15.25
Median ± IQR	125.00 ± 19.00	130.00 ± 18.00	126.00 ± 18.00	141.00 ± 21.00	127.00 ± 18.00
DBP (mmHg)					
Mean ± SD	75.63 ± 7.26	76.60 ± 7.36	76.06 ± 7.09	77.07 ± 9.40	76.15 ± 7.34
Median ± IQR	75.00 ± 9.00	76.00 ± 10.00	76.00 ± 9.00	76.00 ± 13.00	76.00 ± 10.00
Creatinine (µmol/l)					
Mean ± SD	97.67 ± 291.46	99.51 ± 61.78	94.90 ± 205.44	139.98 ± 117.00	98.69 ± 199.89
Median ± IQR	80.23 ± 18.01	92.08 ± 19.99	85.74 ± 20.39	99.90 ± 41.49	86.55 ± 21.49
Total Cholesterol					
Mean (mmol/l) ± SD	4.85 ± 0.91	5.33 ± 17.16	5.12 ± 13.38	5.10 ± 0.96	5.12 ± 12.80
Median (mmol/l)	4.81± 1.16	4.64 ± 0.86	5.10 ± 0.96	5.07 ± 1.20	4.70 ± 1.10
HDL (mmol/l)					
Mean ± SD	1.62 ± 0.55	1.52 ± 3.50	1.56 ± 2.72	1.60 ± 0.58	1.57 ± 2.62
Median ± IQR	1.56 ± 0.53	1.35 ± 0.42	1.43 ± 0.47	1.46 ± 0.75	1.43 ± 0.48
TG (mmol/l)					
Mean ± SD	1.54 ± 3.04	1.74 ± 3.20	1.65 ± 3.25	1.68 ± 1.05	1.65 ± 3.13

Median ± IQR	1.21 ± 0.80	1.32 ± 0.93	1.27 ± 0.82	1.38 ± 0.98	1.28 ± 0.83
LDL (mmol/l)					
Mean ± SD	2.73 ± 0.81	3.13 ± 12.13	3.04 ± 9.37	3.11 ± 0.98	3.05 ± 9.02
Median ± IQR	2.69 ± 1.03	2.60 ± 1.01	2.60 ± 1.00	3.21 ± 1.40	2.63 ± 1.05
TC/HDL ratio					
Mean ± SD	3.22 ± 0.97	4.03 ± 12.49	3.67 ± 9.66	3.60 ± 1.24	3.66 ± 9.30
Median ± IQR	3.03 ± 1.15	3.36 ± 1.14	3.22 ± 1.14	3.44 ± 1.47	3.23 ± 1.16
LDL/HDL ratio					
Mean ± SD	1.81 ± 0.69	2.52 ± 9.57	2.20 ± 7.39	2.17 ± 1.03	2.20 ± 7.11
Median ± IQR	1.70 ± 0.89	1.90 ± 0.88	1.79 ± 0.86	2.04 ± 1.40	1.81 ± 0.90
Serum HbA_{1c} (%)					
Mean ± SD	8.84 ± 1.69	9.65 ± 8.57	9.35 ± 21.02	8.66 ± 1.42	9.29 ± 20.12
Median ± IQR	8.73 ± 2.00	8.57 ± 2.00	8.64 ± 2.00	8.48 ± 2.00	8.62 ± 2.00
Plasma glucose					
Mean (mmol/l) ± SD	10.69 ± 26.52	12.07 ± 44.71	11.66 ± 39.37	9.26 ± 4.31	11.45 ± 37.69
Median(mmol/l) ± IQR	8.82 ± 6.53	9.59 ± 5.90	9.26 ± 6.25	8.84 ± 6.14.	9.22 ± 6.30
Serum Albumin levels					
Mean ± SD	3.05 ± 6.51	3.16 ± 8.50	2.94 ± 7.09	5.34 ± 13.01	3.11 ± 7.68
Median	2.19 ± 1.45	1.95 ± 1.38	2.01 ± 1.28	3.00 ± 1.74	2.06 ± 1.42
TSH					
Mean ± SD	2.71 ± 3.14	2.42 ± 5.79	2.54 ± 4.94	2.70 ± 2.46	2.55 ± 4.78
Median ± IQR	2.00 ± 1.60	1.76 ± 1.10	1.84 ± 1.30	1.99 ± 1.90	1.85 ± 1.40
Body Mass Index(kg/m^2)					
Mean ± SD	26.49 ± 4.86	25..94 ± 5.04	26.12 ± 4.91	27.17 ± 5.34	26.19 ± 4.95
Median ± IQR	25.50 ± 5.60	25.50 ± 4.90	25.50 ± 5.10	25.85 ± 6.10	25.50 ± 5.20

4.2 Population density and age profile

The population profile of those with T1D in the Wirral is observed in Figure 4.1. The age and sex distribution revealed a sinusoidal pattern with an initial peak (Figure 4.1) at the age group 10-14, another peak in the age group 20-24, a plateau between the age groups 30-34 and 35-39. The proportions of males were higher in all age groups except in one age groups this was in the age group 5-9 years. Females were more in the age group 5-9 years.

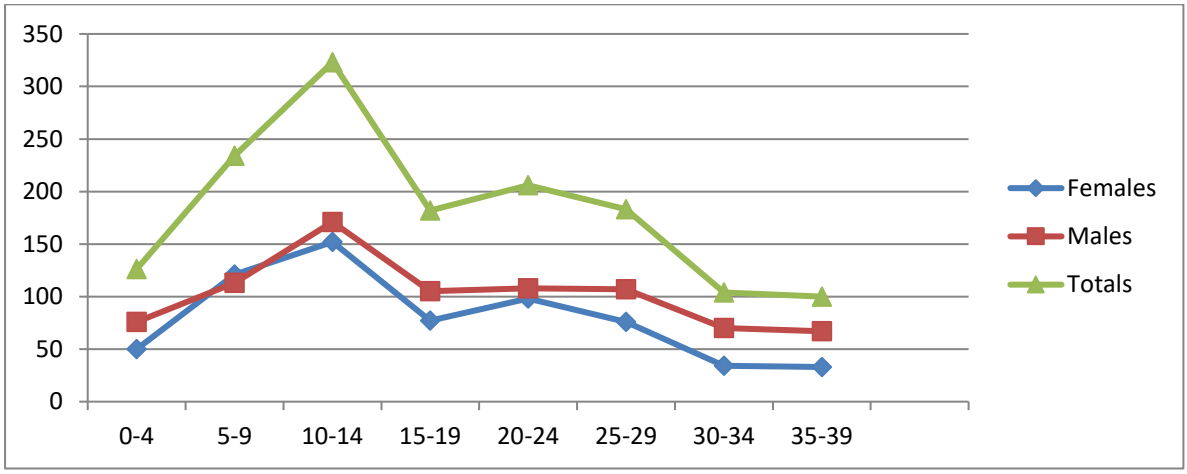


Figure 4.1: Age and sex distribution of people with T1D in the Wirral

The Age- and sex-specific mortality and survival distribution in people with T1D in the Wirral are reflected in Table 4.2. There were more males 817 (56.04%) than females 641 (43.96%).

This observed trend was also reflected in survivors and non-survivors populations with 760 (52.13%) males, 585 (40.12%) females; and 57 (3.90%) males, 56 (3.84%) females respectively.

In the survivor population, the age groups below the age of 30 accounted for majority of the population, the population distribution in this group followed a sinusoidal pattern with a spike in the age group 10 – 14 years, and a gradual decline was noticed after the age of 30 years.

For the non-survivor population, the pattern reflected a sinusoidal pattern with six (6) age groups, 10-14, 15-19, 20-24, 25-29, 30-34, and 35-39 accounting for major proportions in this subset. Although overall gender differentiation in the non-survivor population revealed a higher proportion of males than females, breakdown into age categories showed a mixed picture with females having higher proportions in some age groups. This was evident in age groups 10-14, 25-29, and 35-39

Table 4.2: Age- and sex-specific mortality and survival distribution in people with T1D in the Wirral

Age group (years)	Survivors			Non-Survivors			Overall T1DM		
	Females N (%)	Males N (%)	Total N (%)	Females N (%)	Males N (%)	Total N (%)	Females N (%)	Males N (%)	Total N
0 – 4	49 (8.4)	73 (9.6)	122 (9.1)	1 (1.8)	3 (5.3)	4 (3.5)	50 (7.8)	76 (9.3)	126 (8.6)
5 – 9	119 (20.3)	108 (14.2)	227 (16.9)	2 (3.6)	5 (8.8)	7 (6.2)	121 (18.9)	113 (13.8)	234 (16.0)
10 – 14	141 (24.1)	165 (21.7)	306 (22.8)	11 (19.6)	6 (10.5)	17 (15.0)	152 (23.7)	171 (20.9)	323 (22.2)
15 – 19	72 (12.3)	95 (12.5)	167 (12.4)	5 (8.9)	10 (17.5)	15 (13.3	77 (12.0)	105 (12.9)	182 (12.5)
20 – 24	86 (14.7)	95 (12.5)	181 (13.5)	12 (21.4)	13 (22.8)	25 (22.1)	98 (15.3)	108 (13.2)	206 (14.1)
25 – 29	64 (10.9)	101 (13.3)	165 (12.3)	12 (21.4)	6 (10.5)	18 (15.9)	76 (11.9)	107 (13.1)	183 (12.6)
30 – 34	30 (5.1)	61 (8.0)	91 (6.8)	4 (7.1)	9 (15.8)	13 (11.5)	34 (5.3)	70 (8.6)	104 (7.1)
35 – 39	24 (4.1)	62 (8.2)	86 (6.4)	9 (16.1)	5 (8.8)	14 (12.4)	33 (5.1)	67 (8.2)	100 (6.9)
Total	585(40.12)	760(52.13)	1345(92.25)	56(3.84)	57(3.90)	113(7.75)	641(43.96)	817(56.04)	1458

4.3 Epidemiology: incidence and prevalence

The incidence rate for T1D population in the Wirral followed a sinusoidal pattern during the follow-up period of 12 years. The lowest incidence was in 2011 which was less than 2.18 per 1,000,000, and the highest rate was in 2003 was 15.0 per 1,000,000. Table 4.3 and Figure 4.2 detailed the yearly incidence and prevalence rates with gender differentiation. Although there was witnessed fluctuation in the incidence rates, there was a sustained increase in the prevalence of T1D. The overall prevalence was 10.9 per 1,000,000 but increased to 113.8 per 1,000,000 in 2011. A similar trend was noticed in gender differentiation, but the greatest increase was noticed in males with an increase in the prevalence of almost 150% from 2000 to 2011.

Table 4.3: Annual incidence and prevalence rates per 100000 populations of T1D in the Wirral

Calendar year	Incidence rate			Prevalence rate		
	Females	Males	Total	Females	Males	Total
2000	7.2	23.0	11.0	7.2	15.0	10.9
2001	8.4	18.0	13.0	15.7	32.5	23.8
2002	11.4	14.0	13.0	27.1	46.8	36.6
2003	10.8	20.2	15.0	38.0	67.0	51.9
2004	10.8	13.0	12.0	48.8	80.0	63.8
2005	7.8	13.7	10.6	56.6	91.1	74.4
2006	5.4	11.7	8.4	60.2	105.0	82.9
2007	9.6	11.1	10.0	69.9	116.0	93.2
2008	9.6	15.0	12.2	79.5	131.0	99.4
2009	3.6	9.1	6.25	83.1	140.0	106.0
2010	6.0	10.4	8.13	89.2	151.0	113.8
2011	1.8	2.6	2.18	91.0	153.0	116.0

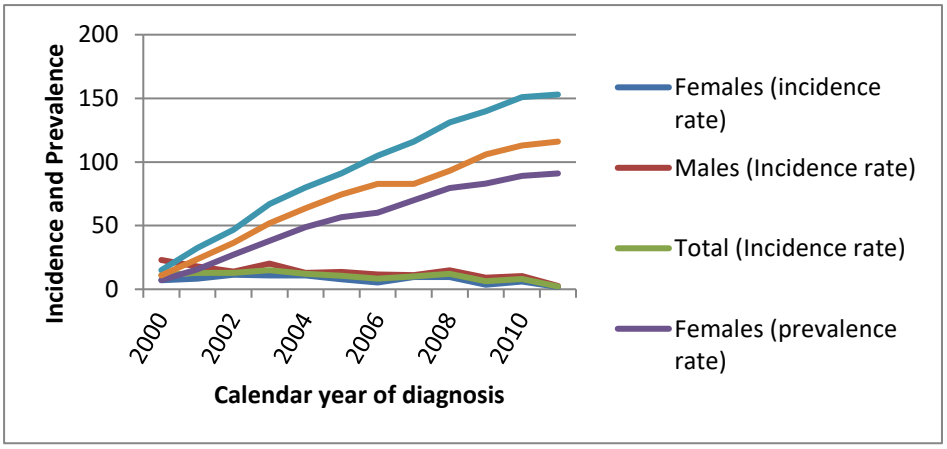


Figure 4.2: Annual incidence and prevalence rates per 100000 population of T1D in the Wirral

4.4 Absolute risk (Probability (risk) of mortality), relative risk and regression analysis

During the follow-up period, the risk of mortality per calendar of diagnosis (explained by the risk of mortality over the entire study duration, given specified entry into a particular calendar year and not the risk of death in the certain year) was found to follow a non-linear pattern (Table 4.4). The overall risk of mortality for the total population of T1D remained stable within the study period. The highest overall risk of mortality was recorded in 2004 which was 0.05 (5%). There were minimal observed variations with gender, details of the risk of mortality by year and differentiated by gender is further reflected in Table 4.4

Table 4.4: Risk of mortality per the calendar year of diagnosis in females, males and overall T1D population in the Wirral

Calendar Year	Risk of Mortality		
	Females	Males	Total T1DM
2000	-	-	-
2001	-	-	-
2002	0.05	0.04	0.04
2003	0.10	-	0.04
2004	0.10	-	0.05
2005	-	-	-
2006	-	0.05	0.04
2007	-	-	-
2008	0.06	-	0.03
2009	-	-	-
2010	-	-	-
2011	-	-	-
2012	-	-	-
Total	0.04	0.01	0.02

The summarised risk of mortality and the corresponding relative risk of specific predicting factors in T1D population of the Wirral are illustrated in Table 4.5. Relative risk (Risk ratio) in this context is defined as a comparison to evaluate the probability of death in each group rather than an estimate for the odds ratio. These values are illustrated in Table 4.5

Running a multiple regression model to evaluate the multiple independent variables against the age at death/censoring for this cohort showed that 89.1% (R^2=0.891) of the variance of the mortality can be explained by the predictor variables evaluated. The result indicate that the model was a significant predictor of mortality in this cohort F (19, 747) =331.72, p= <0.0001. The multiple regression model showed that the significant predictor variables for mortality in this cohort (p-value <0.05) were the age at diagnosis, duration of diagnosis, HbA_{1c}, SBP, DBP, and triglyceride (TG) levels (Table 4.5).

The risk of mortality by gender differentiation showed that males had a lesser risk of mortality than females with values of 0.01 (1%) and 0.04 (4%), females had a high probability of death with a relative risk of four (4) times compared to males.

Table 4.5: Probability (risk) of mortality and relative risk associated with specific predicting factors in T1D including multiple regression analysis to determine significant predictors of mortality

Predicting Factors	**Probability (risk) of mortality**	**Relative Risk**	**Unstandardized B and (P-values) from multiple regression model**
Sex			-0.80 (0.073)
Females	0.04	4	
Males	0.01	1	
Age at diagnosis			0.42(<0.0001)
0 – 4	0.03	1.0 (reference group)	
5 – 9	0.03	1	
10 – 14	0.05	1.7	
15 – 19	0.08	2.7	
20 – 24	0.12	4	
25 - 29	0.1	3.3	
30 – 34	0.13	4.3	
35 – 39	0.14	4.7	
Duration of Diabetes (years)			8.25(<0.0001)
01-10	0.03	1.0 (reference group)	
11-20	0.04	1.3	
21-30	0.05	1.6	
31-40	0.07	2.3	
41-50	0.16	5.3	
BMI (kg/m^2)			0.14(0.588)
≤18.4	-	-	
18.5 - 24.9	0.08	1.1	
25.0 - 29.9	0.07	1.0 (reference group)	
30.0 - 34.9	0.08	1.1	
35.0 - 39.9	0.19	2.7	
≥ 40	0.2	2.9	
IMD			0.13(0.35)
Quintile 1 (most deprived)	0.09	1.5	
Quintile 2 (above average)	0.07	1.2	
Quintile 3 (average)	0.06	1.0 (reference group)	
Quintile 4 (below average)	0.1	1.6	
Quintile 5 (least deprived)	0.08	1.3	
Serum creatinine (µmol/l)			-0.14(0.66)
< 61	0.03	0.5	

62-106	0.06	1.0 (reference group)	
107-129	0.18	3	
130-149	0.4	6.7	
≥ 150	0.4	6.7	
HbA_{1c} %(mmol/mol)			-0.19(0.041)
≤ 5.9 (41)	0.25	8.3	
6.0-6.4(42-46)	0.03	1.0 (reference group)	
6.5-6.9(48-52)	0.06	2	
7.0-7.4(53-57)	0.1	3.3	
7.5-8.0(58-64)	0.06	2	
8.1-8.4(65-68)	0.1	3.3	
8.5-9.0(69-75)	0.07	2.3	
9.1-9.4(76-79)	0.1	3.3	
9.5-10(80-86)	0.07	2.3	
≥ 10.1	0.08	2.6	
SBP (mmHg)			5.16(<0.0001)
≤ 99	-	-	
100 – 119	0.03	1.0 (reference group)	
120 – 139	0.06	2	
140 – 159	0.23	7.7	
≥160	0.35	11.6	
DBP (mmHg)			-2.88(<0.0001)
≤59	0.38	5.4	
60-69	0.11	1.6	
70 – 79	0.07	1.0 (reference group)	
80 – 89	0.1	1.4	
90- 99	0.18	2.6	
≥100	0.3	4.3	
TSH levels (mU/L)			0.33(0.625)
≤0.4	0.15	1.9	
0.4-4.0	0.08	1.0 (reference group)	
≥4.0	0.12	1.5	
Total Cholesterol (mmol/l)			0.27(0.421)
≤3.9	0.06	1	
4.0-4.5	0.07	1.2	
4.6-5.2	0.06	1.0 (reference group)	
5.3-6.1	0.11	1.8	
≥6.2	0.24	4	
LDL (mmol/l)			-0.09(0.817)
≤ 2.5	0.05	1.0 (reference group)	
2.6-3.3	0.06	1.2	
3.4-4.1	0.14	2.8	
4.2-4.9	0.17	3.4	
≥ 5.0	0.27	5.4	
HDL (mmol/l)			-0.19(0.665)

0.4-0.7	-	-	
0.8-1.1	0.05	1.0(reference group)	
1.2-1.5	0.07	1.4	
≥ 1.6	0.08	1.6	
TG (mmol/l)			-1.04(0.004)
≤ 1.6	0.07	1.0 (reference group)	
1.7-2.2	0.12	1.7	
≥2.3	0.1	1.4	
TC/HDL ratio			0.35(0.602)
≤ 3.5	0.06	1.0 (reference group)	
3.6-5.0	0.09	1.5	
≥ 5.1	0.13	2.2	
LDL: HDL ratio			-0.83(0.196)
≤1.5	0.05	1.0 (reference group)	
1.6-3.6	0.07	1.4	
≥ 3.7	0.19	2.7	
Smoking status			0.44(0.094)
Never smoked	0.07	1.0 (reference group)	
Smokes	0.08	1.1	
Ex-smoker	0.14	2	

Considering the age of diagnosis, the age groups 0-4, and 5-9 years had the least risk of mortality of 0.03 (3%). Below the age of 30 years, the highest risk of mortality was recorded in the age group 20-24 years. The highest risk of mortality for this cohort was recorded in the age group 35-39 years with a value of 0.14 (14%), there was a gradually increasing trend of the risk of mortality up till the age group 20-24 years and then a slight decline in the age group 25-29 years 0.10 (10%), then a gradual increase in the age groups of 30-34, and 35-39 years. This is also reflected in the relative risk as there is an initial gradual increase in the probability of death as age increased up to the age group 20-24 years. There was a minor dip in the relative risk age group 25-29 years, which had a relative risk of 3.3 times compared to those 0-4 years. The highest risk of death was recorded in the age group 35-39 years which was 4.7 times that of age group 0-4 years.

The duration of diabetes had various subgroups that experienced varying degrees in the risk of mortality. Those with the condition between 1 and 10 years had the lowest risk of mortality 0.03 (3%). Increase in the duration of diabetes saw a corresponding increase in the risk of mortality with a duration of diabetes between 41-50 years having the highest risk of mortality of 0.16 (16%). For the relative risk, there was increase in the probability of death with increasing duration of T1D. Having T1D for between 11 and 20 years conferred a relative risk

of 1.3 times and having T1D for between 31 and 40 years had a relative risk of 2.4. Above 40 years' duration of T1D had a relative risk of 5.3 times was observed as compared to those less than 10 years' duration.

Being obese (BMI 30 and 39.9) and severely obese (BMI 40 or more) had relative risks of 2.7 times and 2.9 times the probability of death when compared to the reference group of BMI 25.0 - 29.9kg/m^2. For the index of multiple deprivations (IMD), the risk of mortality was most prominent in the group below average for IMD, being 0.10 (10%) followed closely by most deprived 0.09 (9%). Those classes as being average had the least risk of mortality of 0.06 (6%).

Serum creatinine levels of below 61 µmol/l had the lowest risk of mortality 0.03 (3%), in comparison, there was a persistent rise in the risk of mortality as serum creatinine levels rose with the highest risk of 0.40 (40%) at levels of between 130-149 and above 150 µmol/l. Using normal serum creatinine levels (62-106 µmol/l) as the reference, there was a significant increase in the relative risk of mortality with increasing serum creatinine levels. This is observed in table 5.5, those with serum creatinine levels of 107-129 µmol/l (mild; stage 2 CKI, equivalent to GFR 45-89ml/min/1.73m^2), 130-149 µmol/l (moderate; stage 3 CKI, equivalent to GFR 30-45ml/min/1.73m^2), and ≥ 150 µmol/l (severe; stage 4 and 5 CKI, equivalent to GFR <30ml/min/1.73m^2), had 3 times, 6.7 times and 6.7 times the probability of mortality than those within normal creatinine levels.

For glycaemic control, the reference group was glycaemic values of 6.0-6.4% (42-46) mmol/mol. The highest risk of mortality was recorded with values of less than ≤ 5.9% (41) mmol/mol having a value of 0.25 (25%). Levels greater or equal to 10.1% (≥87mmol/mol). Similar levels of risk of mortality 0.10 (10%) was recorded for levels of 7.0-7.4% (53-57) mmol/mol and 8.1-8.4% (65-68) mmol/mol. There was minimal difference in relative risk of mortality between the groups as compared to the reference group (6.5-6.9% [48-52 mmol/mol]). However, there was a significant risk of mortality when glycaemic levels were below 5.9% [≤41 mmol/mol]). Values of (8.1-8.4% [65-68 mmol/mol]) and ≥ 10.1% (≥ 87mmol/mol) respectively had 3.3 times, and 1.6 times the probability of death in comparison to the reference value.

Systolic blood pressure (SBP) of levels between 100 and 119 mmHg were associated with the lowest risk of mortality of 0.03 (3%) while values above or equal to 160 mmHg had the highest risk of mortality 0.35 (35%). Increase in the values for systolic blood pressures was associated with increasing risk of mortality. For diastolic blood pressure (DBP), values less than or equal

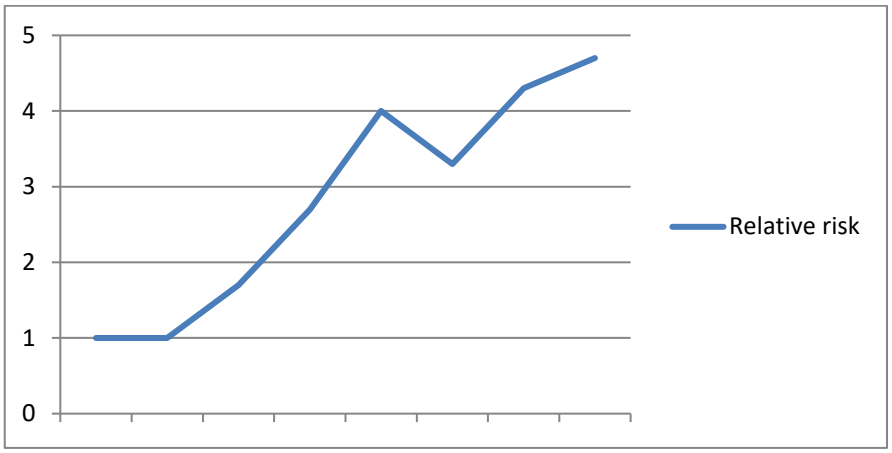
to 59 mmHg had the highest risk of mortality 0.38 (38%). Values above or equal to 100 mmHg also had high risk of mortality 0.30 (30%). The relative risk of death significantly increased with rise in systolic blood pressure (SBP), the relative risk of mortality was 2 times, 7 times and 11.6 times for those with SBP of 120 – 139 mmHg, 140 – 159 mmHg, and ≥160 mmHg respectively as compared to the reference group (100 – 119 mmHg). Conversely, this trend was not noted with diastolic blood pressure (DBP); however, the two extremes (≤59 mmHg [RR: 5.4]) and (≥100 mmHg [RR: 4.3]) of DBP had high relative risk of mortality when compared to the reference group (70-79 mmHg).

TSH levels below or equal to 0.4 mU/L conferred the greatest risk of mortality 0.15 (15%) while those with values of 4.0 mU/L or greater had higher risk of mortality 0.12 (12%) than with those having values 0.4-4.0 mU/L 0.08 (8%).

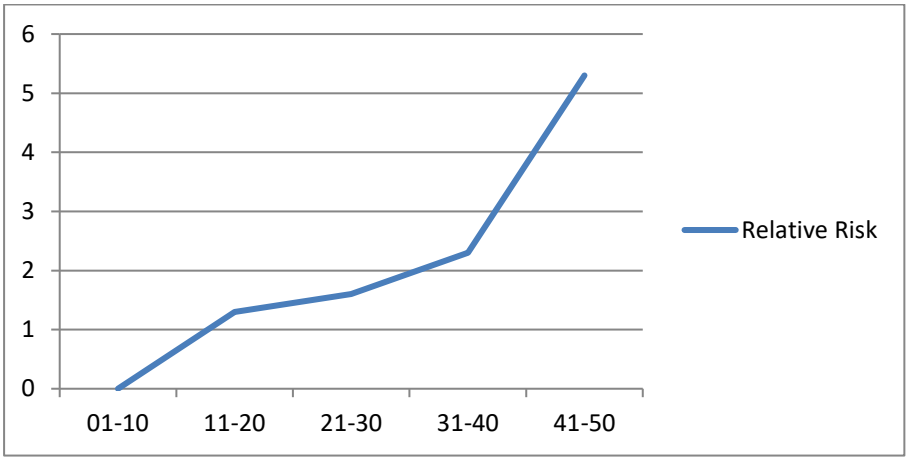
Lipid profiles illustrated varying degrees for risk of mortality. Total cholesterol levels of ≥ 6.2 mmol/l had the highest risk of mortality 0.24 (24%). Higher risk of mortality 0.11 (11%) was also found for values between 5.3-6.1mmol/l. There was minimal difference between the other subgroups. The relative risks for total cholesterol levels were similar for lower levels of total serum cholesterol (≤3.9 mmol/l, 4.0-4.5 mmol/l, and 4.6-5.2 mmol/l [reference group]), however, higher levels of total cholesterol (5.3-6.1 mmol/l and ≥6.2 mmol/l) reflected increased relative risk of 1.8 and 4.0 respectively.

LDL level reflected an increase in the risk of mortality with rising LDL levels. The lowest risk of mortality 0.05 (5%) was found with levels ≤ 2.5 mmol/l while the highest risk of mortality was identified in those who had LDL levels ≥ 5.0 mmol/l. There was little or no differentiation between the various grouping of HDL levels and the greatest risk of mortality 0.08 (8%) was found in those with HDL levels between ≥ 1.6 mmol/l. Reduced levels of serum triglycerides (≤ 1.6 mmol/l) conferred low risk of mortality 0.07 (7%) as compared to the other subgroups. The other subgroups with levels of 1.7-2.2 mmol/l and ≥ 2.3 mmol/l had higher risk of mortality 0.12 (12%) and 0.10 (10%) respectively. TC/HDL ratios reflected increasing risk of mortality with increasing values for ratio. The risk of mortality was highest 0.13 (13%) when the ratio was ≥ 5.1. A similar trend was also noticed with LDL/HDL ratios. The risk of mortality was highest 0.19 (19%) for values greater or equal to 3.7. For smoking status, being an ex-smoker conferred the highest risk of mortality 0.14 (14%). However, current smokers when compared to non-smokers had higher risk of mortality.

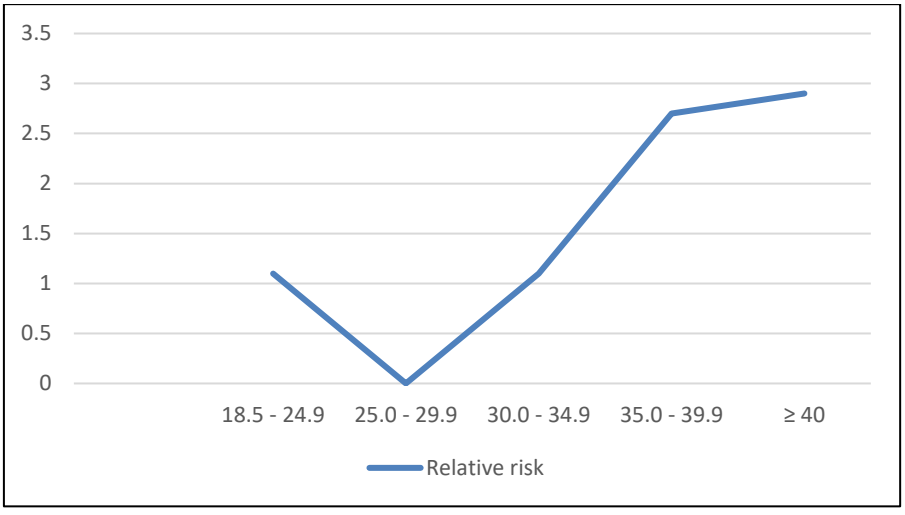
4.5 Graphical representation of the relationship of the predictor variables and mortality risk using RR



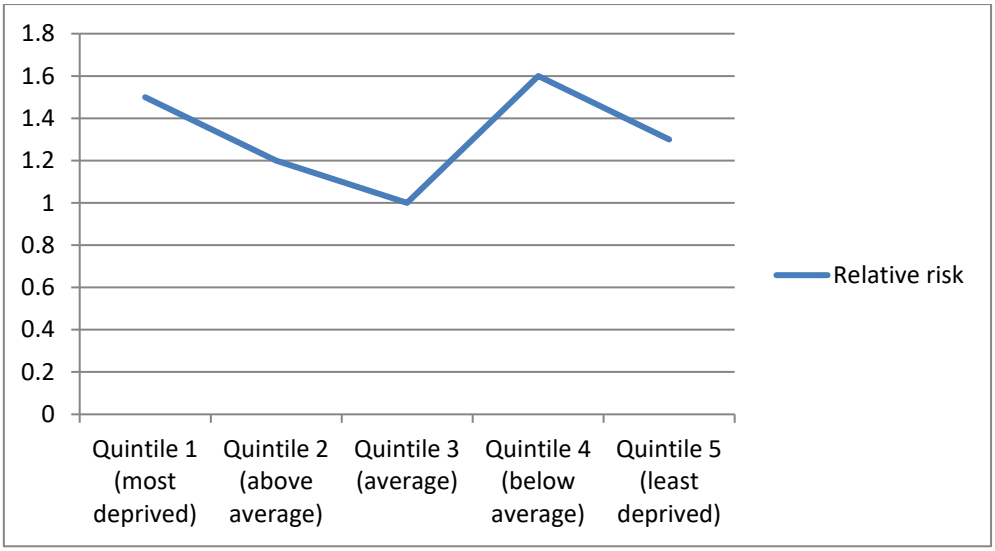
(a) : Age group at diagnosis



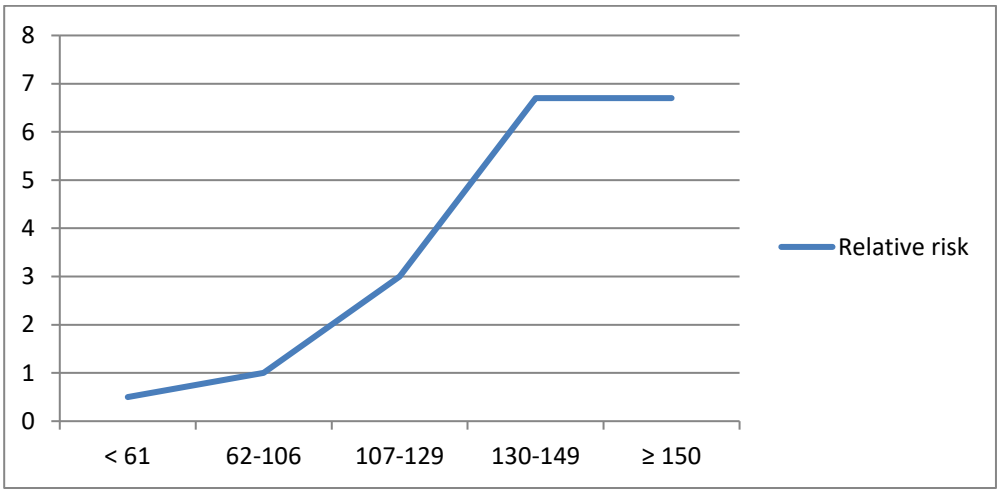
(b): Duration of diabetes (years)



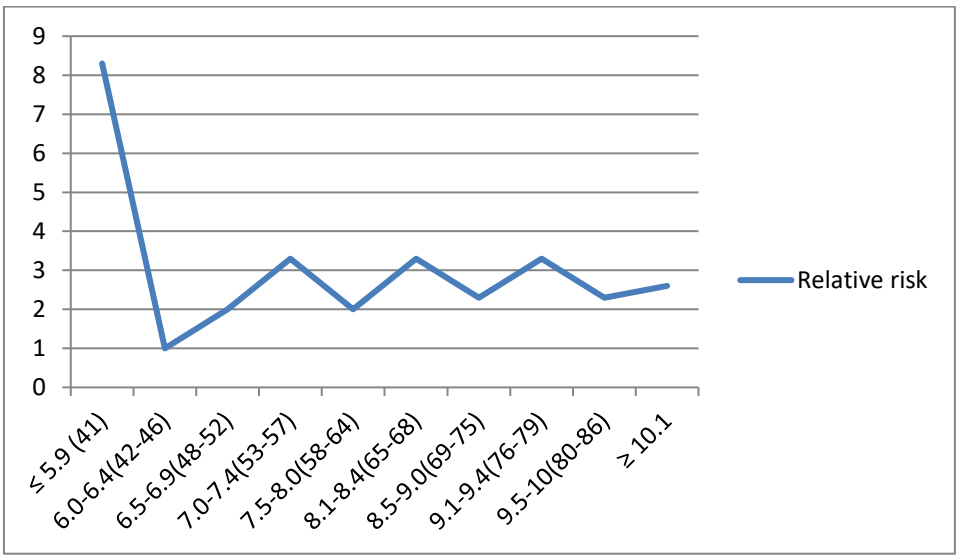
(c) : BMI and relative risk



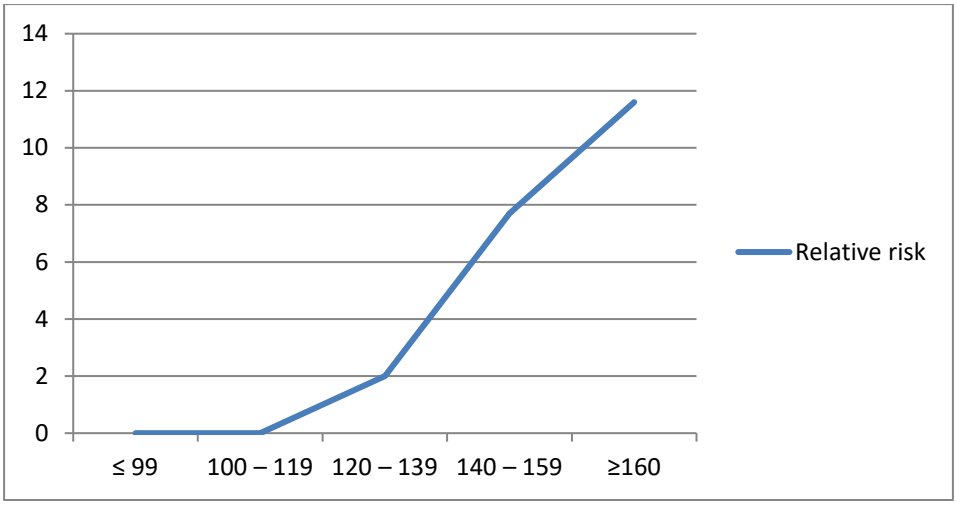
(d): Index of multiple deprivations.



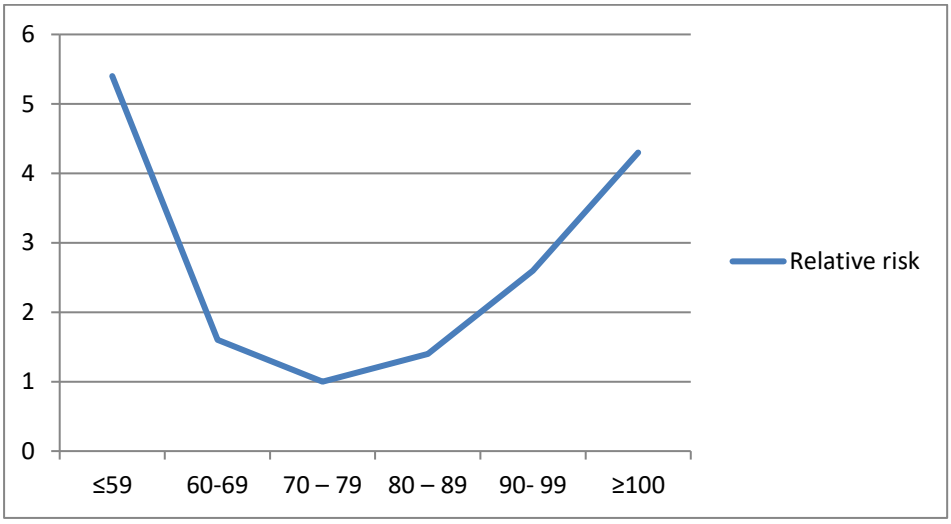
(e): Figure Serum creatinine



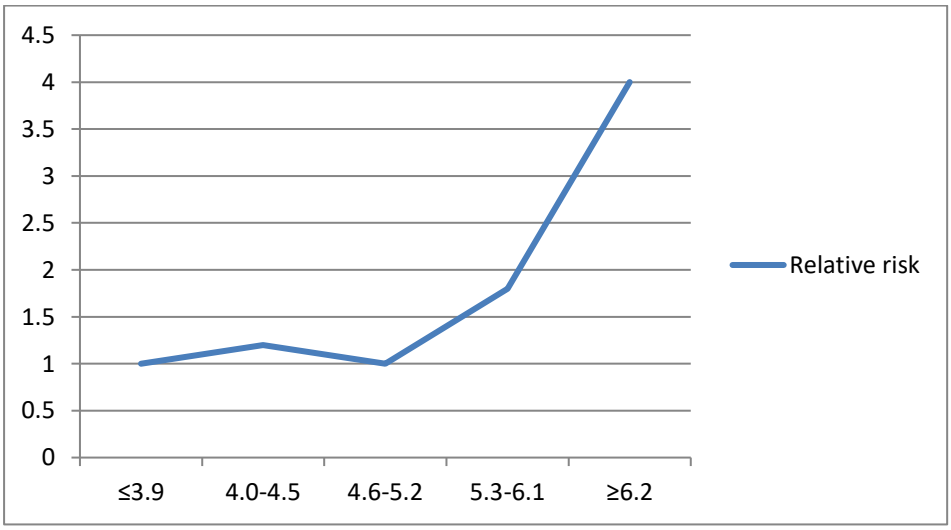
(f): HBA1c



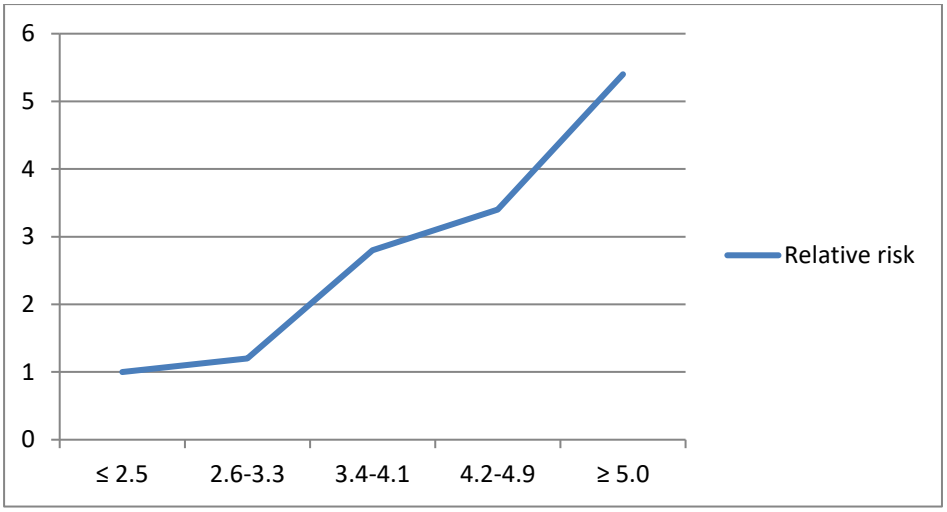
(g): Systolic blood pressure (SBP)mmHg



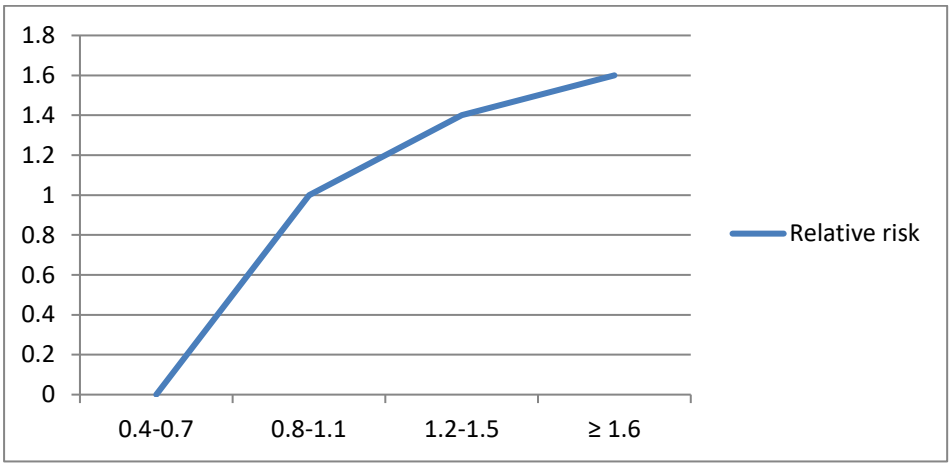
(h): DBP (mmHg)



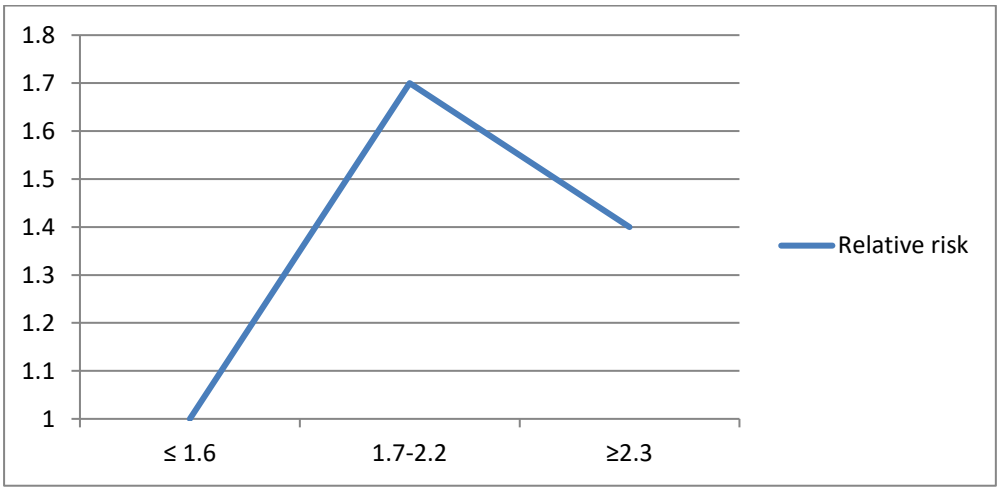
(i): Total Cholesterol (mmol/l)



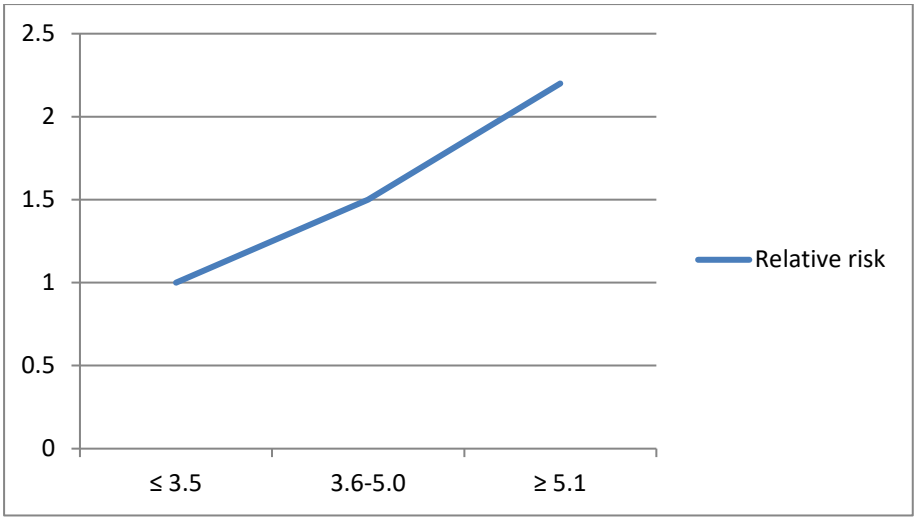
(j): LDL cholesterol (mmol/l)



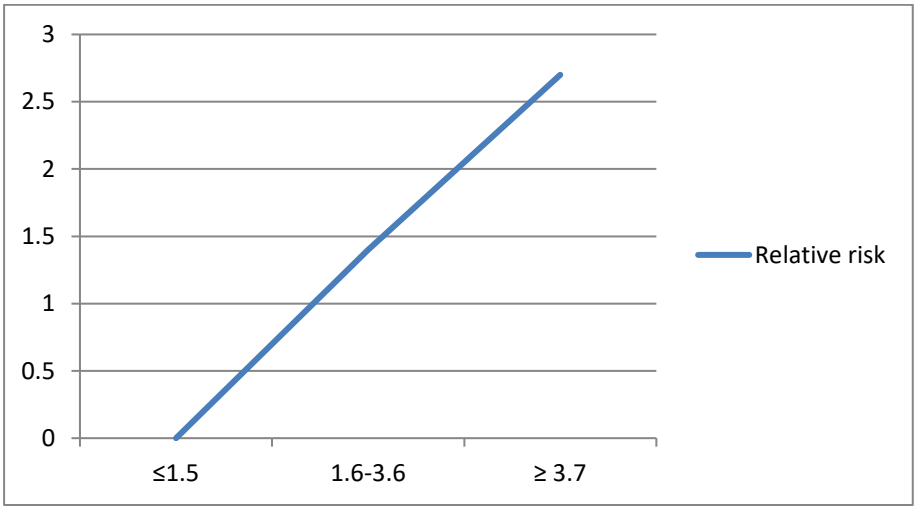
(k): HDL cholesterol (mmol/l)



(l): Triglycerides (mmol/l)



(m): TC:HDL ratio



(n): LDL\HDL Ratio

Figure 4.3(a-n)**:** Representation of the relationship of the predictor variables and mortality risk using RR

4.6 Predicting factors and mortality distribution

4.6.1 Gender

Overall males and females accounted for 817 (56.04%) and 641 (43.96%) respectively. Over the follow-up period, survivors accounted for 1345 (92.25%) of the total T1D population while non-survivors accounted for 113 (7.75%) of the total T1D population. Figure 4.4 illustrates the age and sex stratification of survivors and non-survivors in T1DM population. Chi-squared test was used to determine any significant relationship between the survivors and non-survivors. Of the survivor population (1345), males were more with 760 (52.13%) as compared to females 585 (40.12%). There were 113 non-survivors, 56 (3.84%) were females and 57 (3.90%) were males (p-value <0.0001).

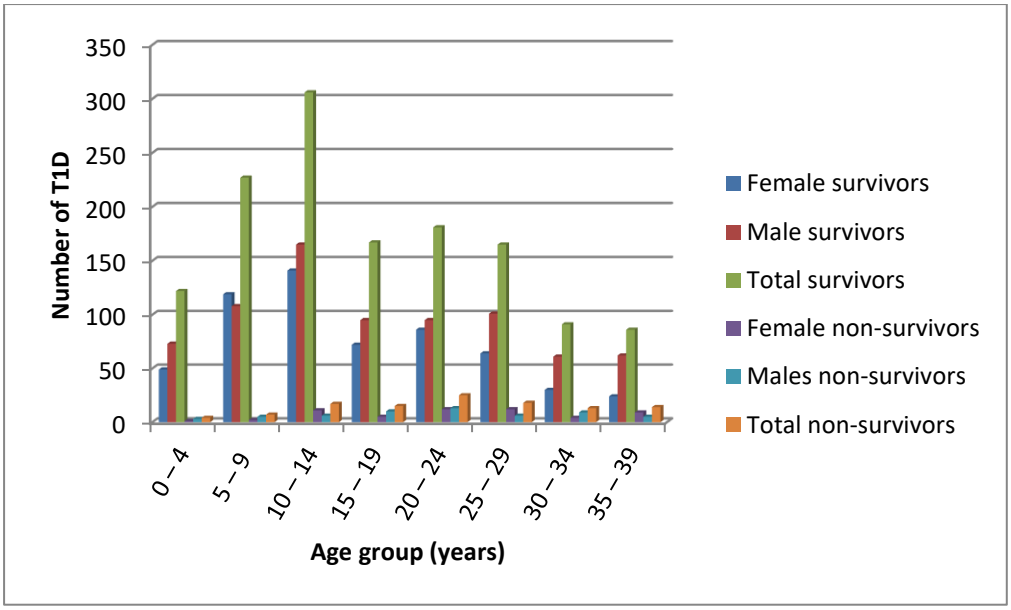


Figure 4.4: Age and sex stratification of survivors and non-survivors in T1D population

Table 4.6 shows the age – and sex-specific distribution among survivors and non-survivors in people with T1D. For those that survived, males were more in all age groups except in the age group 5-9 years, for the non-survivor group, males were more in all groups except age groups 10-14, 25-29, and 35-39 years. In this non-survivor category, females accounted for greater proportions than males 10-14 (19.6:10.5%), 25-29 (21.4%:10.5%), and 35-39 (16.1%:8.8%).

Table 4.6: Age – and sex-specific distribution among survivors, and non-survivors in people with T1D, in the Wirral including chi square test for statistically significant association between survivors and non-survivors.

Age group (years)	**Sex**				**Total T1DM N (%)**	**p-value**
	Females		**Males**			
	Survivors N (%)	**Non-survivors N (%)**	**Survivors N (%)**	**Non-survivors N (%)**		
0 – 4	49 (7.6)	1 (0.2)	73 (9.6)	3 (5.3)	126 (8.6)	
5 – 9	119 (18.6)	2 (3.6)	108 (14.2)	5 (8.8)	234 (16.0)	
10 – 14	141 (24.1)	11 (19.6)	165 (21.7)	6 (10.5)	323 (22.2)	<0.0001
15 – 19	72 (12.3)	5 (8.9)	95 (12.5)	10 (17.5)	182 (12.5)	
20 – 24	86 (14.7)	12 (21.4)	95 (12.5)	13 (22.8)	206 (14.1)	
25 – 29	64 (10.9)	12 (21.4)	101 (13.3)	6 (10.5)	183 (12.6)	
30 – 34	30 (5.1)	4 (7.1)	61 (8.0)	9 (15.8)	104 (7.1)	
35 – 39	24 (4.1)	9 (16.1)	62 (8.2)	5 (8.8)	100 (6.9)	
Total	585	56	760	57	1458 (100)	

4.6.2 Age at diagnosis

Table 4.7 illustrates the categories of the age at diagnosis into various subgroups, and their percentages for survivors, non-survivors, and total T1D population (p-value <0.0001, df =7,

X^2=29.358). Among the survivors, the age group 10-14 years had the highest frequency and then subsequently by the age group 5-9 years. These two age groups jointly accounted for over one-third (36.6%) of the survivor population. Conversely, in the non-survivor group, the 20-24 years' age group had the highest frequency, followed closely by four age groups 25-29 and 10-14 age groups.

Figure 4.5 highlights the age-specific relative risk and risk of mortality in people with T1D in the Wirral. Overall, there was an increase in the relative risk and the risk of mortality as the age of diagnosis (entry into the study) increased.

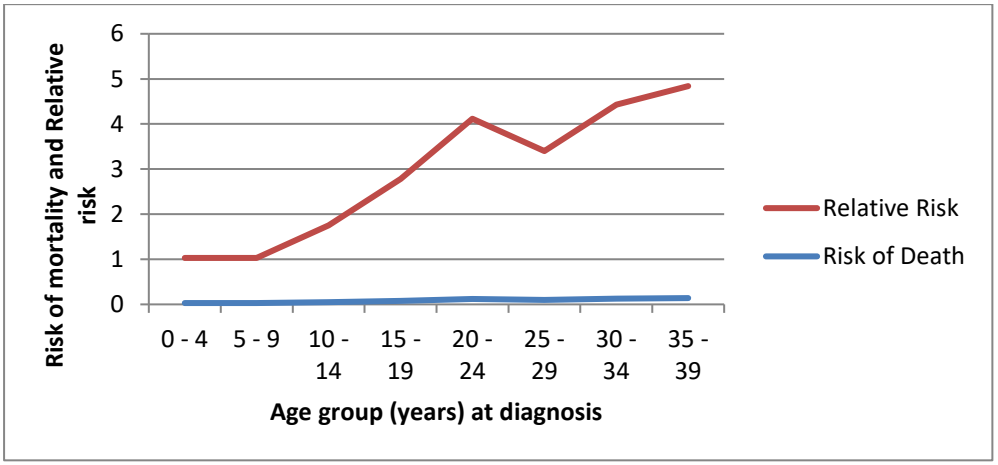


Figure 4.5: Age-specific relative risk and risk of mortality in people with T1D in the Wirral

The risk of mortality followed a linear pattern in increase from 3% in the 0-4 year age group to 14% in the 35-39 year age group. However, for the relative risk, there was an exponential increase in RR from 1 in the 0-4 age group to 4.7 in the 35-39 year age group. This followed a sinusoidal pattern with peaks for the following age groups; 20-24, 30-34, and 35-39 years with corresponding RRs of 4.0, 4.3, and 4.7.

Table 4.7: Basic distribution characteristics for survivors and non-survivors according to age at diagnosis, duration of diagnosis and smoking status including chi square test for statistical significant association between survivors and non-survivors

Characteristics	Survivors N (%)	Non-Survivors N (%)	Total T1DM	p-values
Age at diagnosis (years)				<0.0001
0 – 4	122 (8.4)	4 (0.3)	126 (8.6)	
5 – 9	227 (15.6)	7 (0.5)	234 (16.0)	
10 – 14	306 (21.0)	17 (1.2)	323 (22.2)	
15 – 19	167 (11.5)	15 (1.0)	182 (12.5)	
20 – 24	181 (12.4)	25 (1.7)	206 (14.1)	
25 – 29	165 (11.3)	18 (1.2)	183 (12.6)	
30 – 34	91 (6.2)	13 (0.9)	104 (7.1)	
35 – 39	86 (5.9)	14 (1.0)	100 (6.9)	
Total	1345 (92.2)	113 (7.8)	1458 (100)	
Duration of diabetes (years)				<0.0001
1-10	306 (22.4)	8 (0.6)	314 (23.0)	
11-20	382 (28.0)	14 (1.0)	396 (29.0)	
21-30	275 (20.2)	13 (1.0)	288 (21.1)	
31-40	222 (16.3)	16 (1.2)	238 (17.4)	
41-50	108 (7.9)	20 (1.5)	128 (9.4)	
Total	1293 (94.8)	71 (5.2)	1364 (100)	
Smoking status				0.015
Never smoked	542 (54.4)	43 (4.3)	585 (58.7)	
Ex-smoker	205 (20.6)	32 (3.2)	237 (23.8)	
Current smoker	162 (16.2)	13 (1.3)	175 (17.6)	
Total	909 (91.2)	88 (8.8)	997 (100)	

4.6.3 Smoking

Table 4.7 and Figure 4.6 show the overall distribution of T1D population according to their smoking status, 23.8% and 17.6% were ex-smokers and current smokers respectively. However, considering the non-survivor population, 1.3% were still smoking at the time of their demise, while 3.2% had stopped smoking at the time of death (p-value 0.015, df =2, X^2=8447).

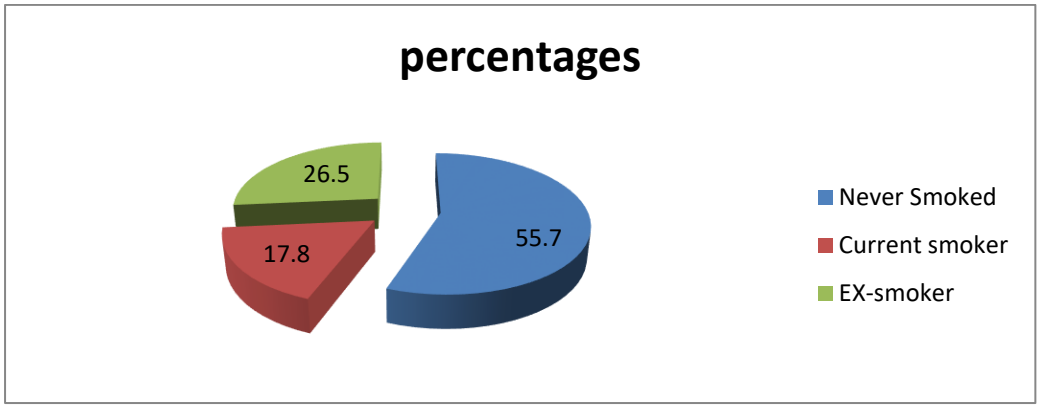


Figure 4.6: Distribution of T1D population according to their smoking status.

3.4.9 Body Mass Index (BMI): Measure of obesity

With the body mass index (BMI), there was increased potential probability (risk) of death found in those in higher categories of BMI 35-39, and ≥ 40 kg/m^2 with values of 0.19 (19%) and 0.20 (20%) respectively.

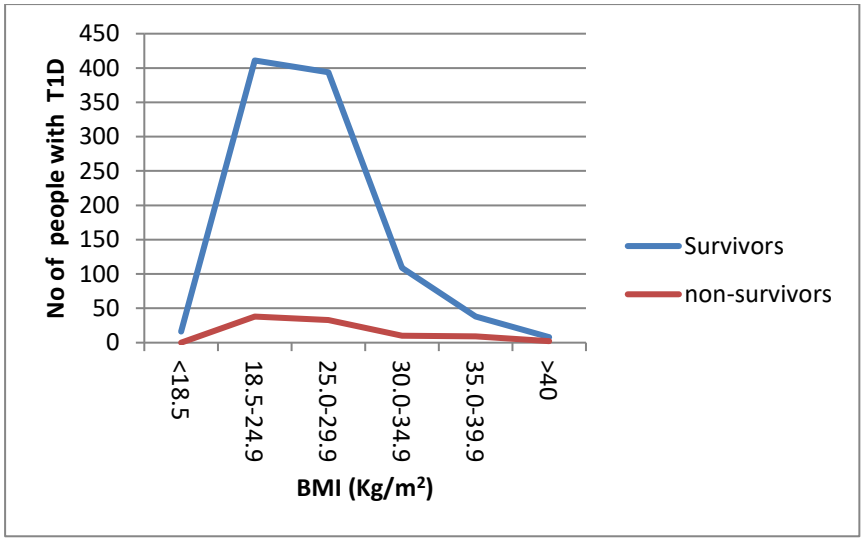


Figure 4.7: Distribution of survivors and nom-survivors among T1D in the Wirral according to their BMI

The distribution of BMI into survivor and non-survivor categories among T1D in the Wirral as reflected in Figure 4.7 and Table 4.8. Majority of the non-survivors (38 [3.6%]) were found to have normal BMI range. This was followed by those who were overweight (33 [3.1%]) with BMI range 25.0 - 29.9, and then those with class 1 obesity of BMI 30.0-34.9 (10 [0.9 %]). The survivor group showed similar trend as the non-survivors in terms of distribution.

Table 4.8: The characteristics of BMI, HbA_{1c}, and IMD among survivors, non-survivors and total T1D population including chi-square test for statistical significant association between survivors and non-survivors

Characteristics	Survivors N (%)	Non-Survivors N (%)	Total T1DM	p-values
BMI (kg/m^2) 0.069				
<18.5	16 (1.5)	0 (0)	16 (1.5)	

18.5-24.9	411 (38.5)	38 (3.6)	449 (42.0)	
25.0-29.9	394 (36.9)	33 (3.1)	427 (40.0)	
30.0-34.9	109 (10.2)	10 (0.9)	119 (11.1)	
35.0-39.9	38 (3.6)	9 (0.8)	47 (4.4)	
>40	8 (0.7)	2 (0.2)	10 (0.9)	
Total	976 (91.4)	92 (8.6)	1068 (100)	
HbA_{1c} % (mmol/mol)				0.295
≤ 5.9 (41)	12 (1.0)	4 (0.3)	16 (1.3)	
6.0-6.4 (42-46)	29 (2.3)	1 (0.1)	30 (2.4)	
6.5-6.9 (48-52)	60 (4.8)	4 (0.3)	64 (5.2)	
7.0-7.4 (53-57)	85 (6.8)	9 (0.7)	94 (7.6)	
7.5-8.0 (58-64)	180 (14.5)	12 (1.0)	192 (15.5)	
8.1-8.4 (65-68)	113 (9.1)	13 (1.0)	126 (10.2)	
8.5-9.0 (69-75)	212 (17.1)	16 (1.3)	228 (18.4)	
9.1-9.4 (76-79)	94 (7.6)	10 (0.8)	104 (8.4)	
9.5-10 (80-86)	140 (11.3)	10 (0.8)	150 (12.1)	
≥ 10.1 (87)	219 (17.6)	18 (1.5)	237 (19.1)	
Total	1144 (92.2)	97 (7.8)	1241 (100)	
IMD (Quintiles)				0.328
1 (most deprived)	415 (27.8)	39 (2.6)	454 (30.4)	
2 (below average)	283 (18.9)	20 (1.3)	303 (20.3)	
3 (average)	192 (12.8)	13 (0.9)	205 (13.7)	
4 (above average)	256 (17.1)	31 (2.1)	287 (19.2)	
5 (least deprived)	226 (15.1)	20 (1.3)	246 (16.5)	
Total	1372 (91.8)	123 (8.2)	1495 (100)	

4.6.4 Glycaemic control

Although the result highlighted no statistical significance of the various deciles for HbA_{1c} (p-value 0.295, df =9, x^2=10.723). The results as illustrated in Table 4.8, with the distribution of survivors and non-survivors in Figure 4.8 indicate that only 11.6% of the survivors, 1% of the non-survivors and 12.8% of the overall population with T1D attained satisfactory levels of control of between 6.0-7.4%.

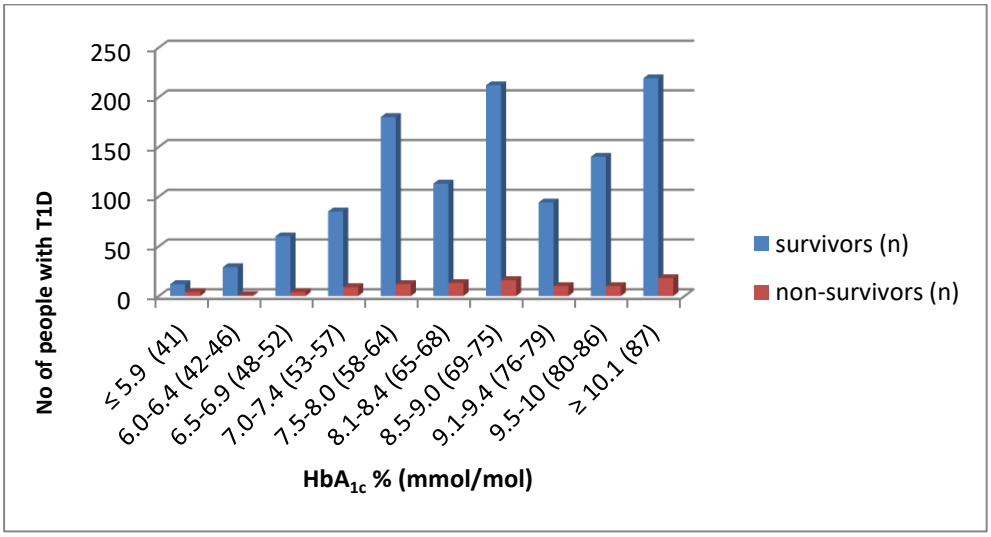


Figure 4.8: Distribution of HbA_{1c} (%) among survivors and non-survivors in T1D

For levels of $HbA_{1c} \leq 5.9\%$ in survivors, non-survivors, and total participants with T1D, were 1.0%, 0.3% and 1.3% respectively. The highest distribution of survivors (17.1%), non-survivors (1.3%), and total cohort (18.4%) attained glycaemic levels of 8.5-9.0%. Also, HbA_{1c} levels $\geq 7.5\%$ was recorded in 77.6%, 6.4%, and 83.7% of survivors, non-survivors, and total T1D population respectively.

4.6.5 IMD (social deprivation)

The results highlighted in table 4.8 indicate that a proportionate number of people with T1D was found in the most deprived quintile (30.4%). A similar trend in distribution was noted in both survivors and non-survivor subgroups with 27.8% and 2.6% respectively. 15.1%, 1.3%, and 16.5% of survivors, non-survivors and total T1D population were noted to be in the least deprived quintile. Figure 4.9 highlights the distribution of survivors and non-survivors in T1D. Almost twice the number of people lived in the most deprived areas as compared to the least deprived areas.

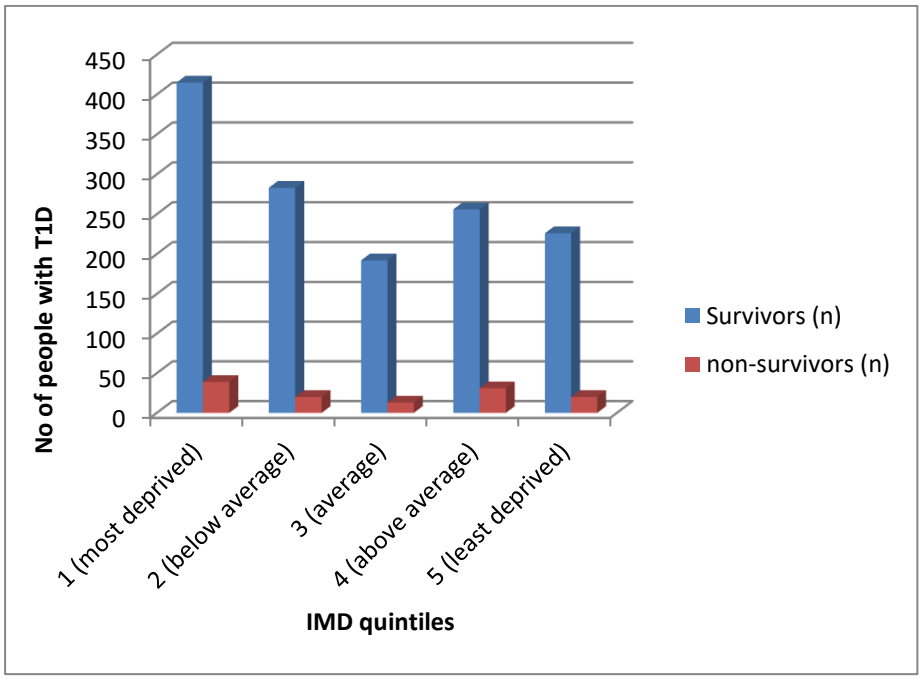


Figure 4.9: Distribution of survivors and non-survivors in T1D according to IMD

4.6.6 Systolic blood pressure (SBP)

Table 4.9 highlights significant statistical relationship between survivors, non-survivors and SBP (p-value <0.0001, df =4, X^2=99.879). More participants in the survivors, non-survivors and total T1D population were found to have higher levels of SBP in the quintile 120-139 mmHg, having 49.7%, 3.2%, and 52.9% respectively. Only 25.4% of survivors, 0.8% of non-

survivors and 26.2% of the total T1D population have normal range of SBP (100-119mmHg). Those noted to be in the hypertensive stage (≥ 140 mmHg) were 15.1% of the survivors, 5.1% of non-survivors, and 20.2% of the total T1D population. Figure 4.10 highlights the distribution of the survivors and non-survivors with T1D in the Wirral according to their SBP (mmHg).

Table 4.9: Distribution of serum creatinine, SBP and DBP amongst the survivors and non-survivors and total T1D including chi square test for statistical significant association between survivors and non-survivors

Characteristics	**Survivors N (%)**	**Non-Survivors N (%)**	**Total T1DM**	**p-values**
SBP (mmHg)				<0.001
≤ 99	8 (0.7)	0 (0)	8 (0.7)	
100–119	279 (25.4)	9 (0.8)	288 (26.2)	
120–139	547 (49.7)	35 (3.2)	582 (52.9)	
140–159	134 (12.2)	40 (3.6)	174 (15.8)	
≥160	31 (2.8)	17 (1.5)	48 (4.4)	
Total	999 (90.8)	101(9.2)	1100 (100)	
DBP (mmHg)				0.001
≤59	5 (0.5)	3 (0.3)	8 (0.7)	
60-69	147 (13.4)	18 (1.6)	165 (15.0)	
70 – 79	555 (50.5)	41 (3.7)	598 (54.2)	
80 – 89	251 (22.8)	29 (2.6)	280 (25.5)	
90- 99	37 (3.4)	8 (0.7)	45 (4.1)	
≥100	4 (0.4)	2 (0.2)	6 (0.5)	
Total	999 (90.8)	101 (9.2)	1100 (100)	
Serum creatinine (µmol/l)				<0.0001
< 61	96 (6.8)	3 (0.2)	99 (7.0)	
62-106	1066 (75.1)	65 (4.6)	1131 (79.6)	
107-129	98 (6.9)	21 (1.5)	119 (8.4)	
130-149	12 (0.8)	8 (0.6)	20 (1.4)	
≥ 150	30 (2.1)	21 (1.5)	51 (3.6)	
Total	1302 (91.7)	118 (8.3)	1420 (100)	

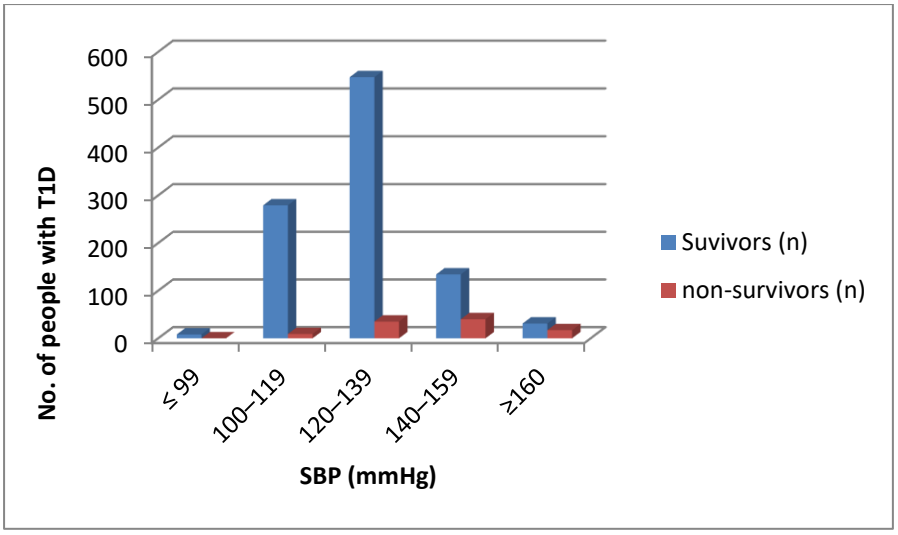


Figure 4.10: Distribution of the survivors and non-survivors with T1D in the Wirral according to their SBP (mmHg)

The quintiles above the normal range for systolic blood pressure (≥ 120mmHg) accounted for most of the participants in the various subgroups of survivors, non-survivor and overall T1D population.

4.6.7 Diastolic blood pressure (DBP)

The distribution of the survivors and non-survivors with T1D in the Wirral according to their DBP (mmHg) is illustrated in Figure 4.11. Table 4.9 shows that the largest cohort of participants had their DBP within 70-79 mmHg range; this is reflected as 50.7% of survivors, 3.7% of non-survivors and 54.2% of the total population of T1D. Slightly lower proportions of survivors, non-survivors, and total T1D population had their DBP within the range 80-89 mmHg. The relationship between DBP and mortality status was statistically significant (p-value: 0.001, df = 5, $X^2 = 20.72$).

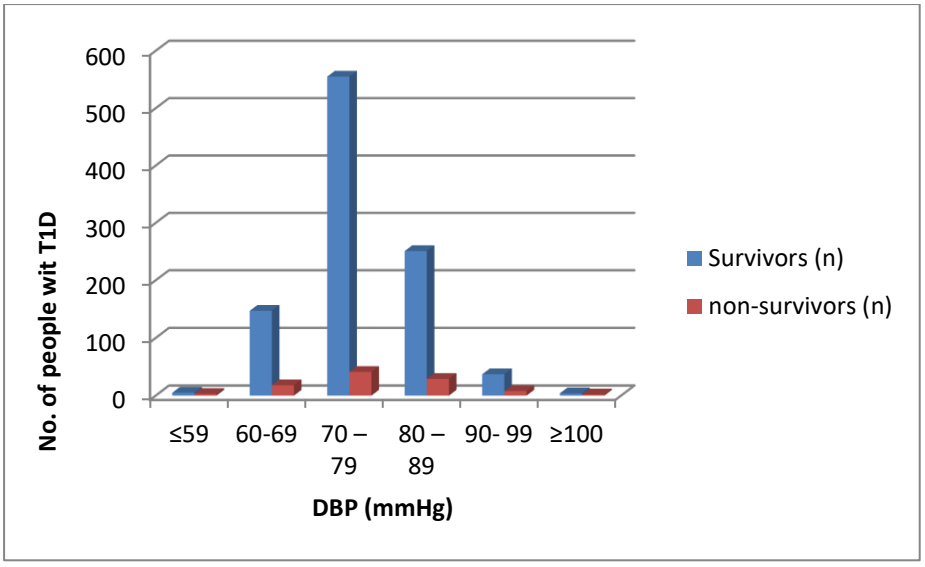


Figure 4.11: Distribution of the survivors and non-survivors with T1D in the Wirral according to their DBP (mmHg)

Majority of the participants in the study had normal diastolic blood pressures.

4.6.8 Serum creatinine and renal status

Figure 4.12 shows the distribution of the survivors and non-survivors with T1D in the Wirral according to their serum creatinine levels (µmol/l). The association between the various subgroups were statistically significant (p-value: <0.001, df = 4, X^2 = 125.65). The largest cohort of T1D had their creatinine levels within the normal range of 62-106 µmol/l; this was reflected as 75.1% of survivors, 4.6% of non-survivors and 79.6% of T1D population.

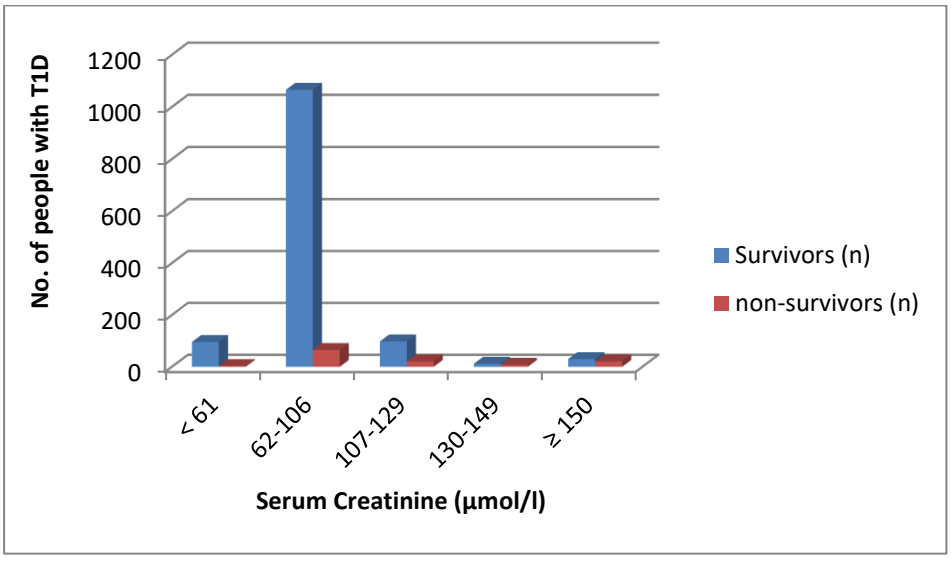


Figure 4.12: Distribution of the survivors and non-survivors with T1D in the Wirral according to their serum creatinine levels (µmol/l)

4.6.9 Total Cholesterol levels (TC)

Figure 4.13 shows the distribution of the survivors and non-survivors with T1D in the Wirral, according to their serum total Cholesterol levels (mmol/l). Those that had serum cholesterol levels ≤ 3.9 mmol/l in the survivor, non-survivor, and total T1D population were 14.6%, 0.9%, and 15.5% respectively. Conversely, Table 4.10 also shows that those who had serum cholesterol levels ≥ 6.2mmol/l in the various subgroups were 4.3% for survivors, 1.3% for non-survivors, and 5.6% for total T1D population. The correlation between the various subgroups and mortality status was also statistically significant (p-value: <0.0001, df = 4, $X^2 = 28.66$).

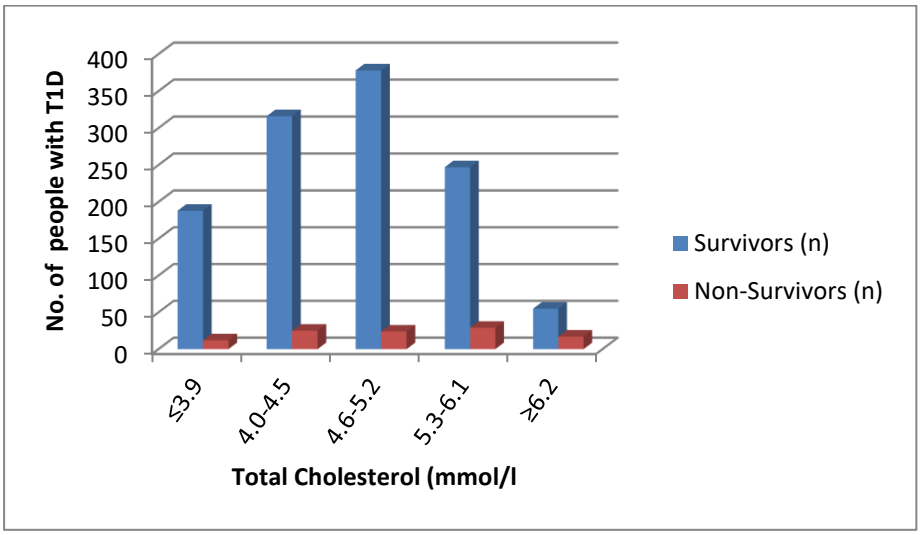


Figure 4.13: Distribution of the survivors and non-survivors with T1D in the Wirral, according to their serum Total Cholesterol levels (mmol/l).

4.6.10 Total Triglycerides (TG)

The distribution of the survivors and non-survivors with T1D in the Wirral, according to their serum Triglyceride (mmol/l) is reflected in Figure 4.14. Table 4.10 shows that the largest cohorts of survivors (66.8%), non-survivors (5.2%) and total T1D populations (72%) had TG levels ≤ 1.6 mmol/l. Correlation between survivors and non-survivors were not statistically significant (p-value:< 0.063, df = 2, $X^2 = 5.54$)

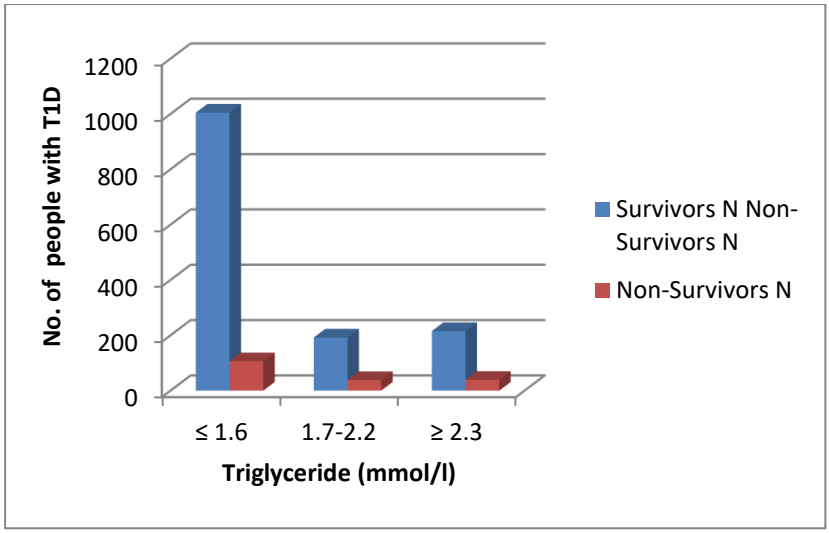


Figure 4.14: Distribution of the survivors and non-survivors with T1D in the Wirral, according to their serum Triglyceride (mmol/l).

Table 4.10: Distribution of TC, TG, HDL, LDL, TC/HDL, LDL/HDL, and TSH amongst survivors, non-survivors, and total T1D population including chi square test for statistical significant association between survivors and non-survivors

Characteristics	**Survivors N (%)**	**Non-Survivors N (%)**	**Total T1D**	**p-values**
Total Cholesterol (mmol/l)				< 0.001
≤3.9	188 (14.6)	12 (0.9)	200 (15.5)	
4.0-4.5	316 (24.5)	25 (1.9)	341 (25.4)	
4.6-5.2	378 (29.3)	24 (1.9)	402 (31.1)	
5.3-6.1	247 (19.1)	29 (2.2)	276 (21.4)	
≥6.2	55 (4.3)	17 (1.3)	72 (5.6)	
Total	1184 (91.7)	107 (8.3)	1291 (100)	
TG (mmol/l)				0.063
≤ 1.6	899 (66.8)	70 (5.2)	969 (72.0)	
1.7-2.2	159 (11.8)	22 (1.6)	181 (13.4)	
≥ 2.3	177 (13.2)	19 (1.4)	196 (14.6)	
Total	1235 (91.8)	111 (8.2)	1346 (100)	
HDL (mmol/l)				0.573
0.4-0.7	5 (0.5)	0 (0)	5 (0.5)	
0.8-1.1	173 (15.6)	10 (0.9)	183 (16.5)	
1.2-1.5	436 (39.4)	32 (2.9)	468 (42.3)	
≥ 1.6	414 (37.4)	37 (3.3)	451 (40.7)	
Total	1028 (92.9)	79 (7.1)	1107 (100)	
LDL (mmol/l)				<0.001
≤ 2.5	567 (45.5)	30 (2.4)	297 (47.9)	
2.6-3.3	406 (32.6)	24 (1.9)	430 (34.5)	
3.4-4.1	156 (12.5)	25 (2.0)	181 (14.5)	
4.2-4.9	20 (1.6)	4 (0.3)	24 (1.9)	
≥ 5.0	11 (0.9)	4 (0.3)	15 (1.2)	
Total	1160 (93.0)	87 (7.0)	1247 (100)	

TC/HDL ratio				0.044
≤ 3.5	790 (60.9)	53 (4.1)	843 (64.9)	
3.6-5.0	343 (26.4)	34 (2.6)	377 (29.0)	
≥ 5.1	68 (5.2)	10 (0.8)	78 (6.0)	
Total	1201 (92.5)	97 (7.5)	1298 (100)	
LDL: HDL ratio				0.022
≤1.5	379 (30.4)	28 (2.2)	407 (32.6)	
1.6-3.6	746 (59.8)	59 (4.7)	805 (64.5)	
≥ 3.7	29 (2.3)	7 (0.6)	36 (2.9)	
Total	1154 (92.5)	94 (7.5)	1248 (100)	
TSH (mU/L)				0.014
≤ 0.4	11 (0.8)	2 (0.1)	13 (1.0)	
0.4-4.0	1124 (82.7)	92 (6.8)	1216 (89.5)	
≥ 4.0	111 (1246)	19 (1.4)	130 (9.6)	
Total	1246 (91.7)	113 (8.3)	1359 (100)	

4.6.11 High-density lipoprotein levels (HDL) levels

Table 4.10 shows the distribution of the survivors, non-survivors, and total T1D population in the Wirral, according to their serum HDL levels. The largest cohort of survivors (39.4%), non-survivors (2.9%) and total T1D population (42.3%) had HDL levels between 1.2-1.5 mmol/l. The smallest proportion of survivors (0.5%), non-survivors (0%) and total T1D population (0.5%) had HDL levels between 0.4-0.7mmol/l. Figure 4.15 highlights the distribution of the survivors and non-survivors with T1D in the Wirral, according to their serum HDL levels (mmol/l).

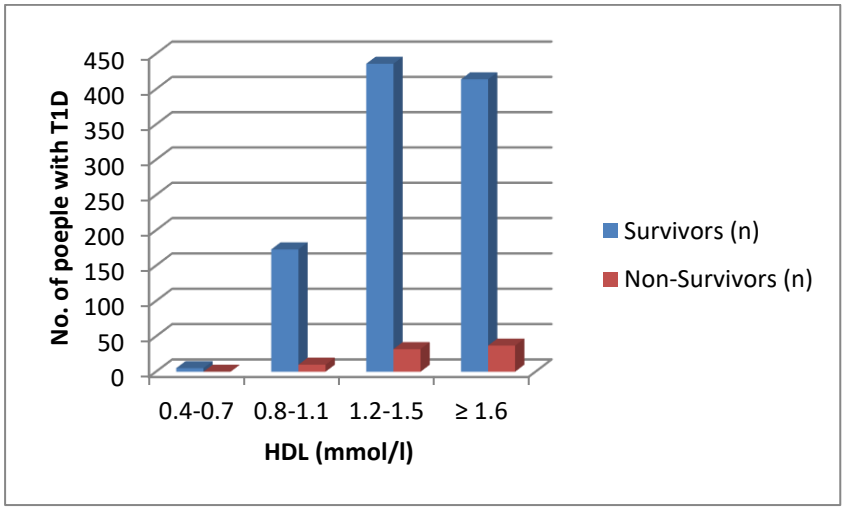


Figure 4.15: Distribution of the survivors and non-survivors with T1D in the Wirral, according to their serum HDL levels (mmol/l).

4.6.12 Low-density lipoprotein levels (LDL) levels

Figure 4.16 shows the distribution of the survivors and non-survivors with T1D in the Wirral, according to their serum LDL levels (mmol/l). It shows a gradual decline in the distribution pattern for non-survivors.

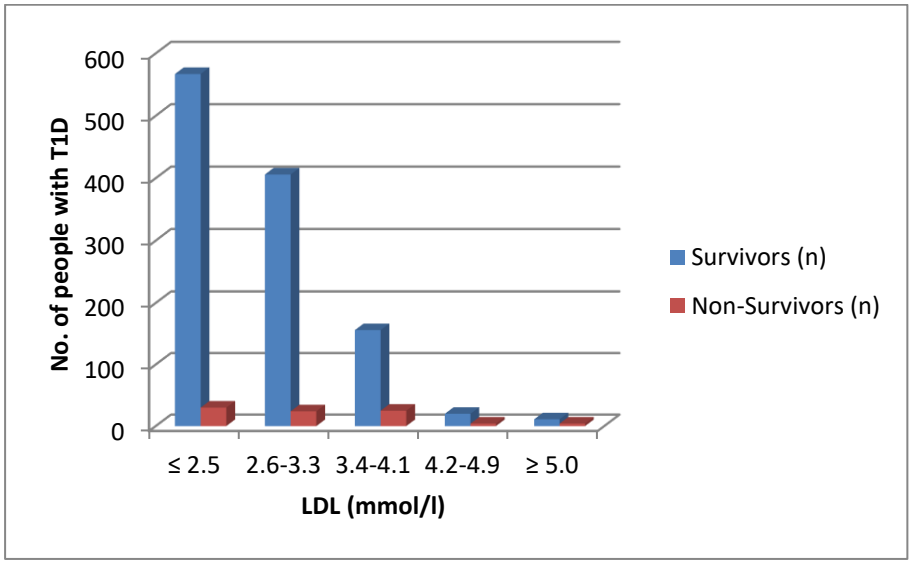


Figure 4.16: Distribution of the survivors and non-survivors with T1D in the Wirral, according to their serum LDL levels (mmol/l)

Table 4.10 shows the distribution of the survivors, non-survivors, and total T1D population in the Wirral, according to their serum LDL levels. The largest cohort of survivors (45.5%), non-survivors (2.4%) and total T1D population (47.9%) had LDL levels ≤ 2.5 mmol/l. Although very small proportions of the survivors (0.9%), non-survivors (0.3%), and total T1D population (1.2%) had LDL levels ≥5.0 mmol/l.

4.6.13 Total Cholesterol to HDL ratio

Figure 4.17 shows the distribution of the survivors and non-survivors with T1D in the Wirral, according to their TC/HDL ratio. Table 4.14 illustrates that 4.1%, 2.6%, and 0.8% of non-survivors had TC/HDL ratios of ≤ 3.5, 3.6-5.0, and ≥ 5.1 respectively.

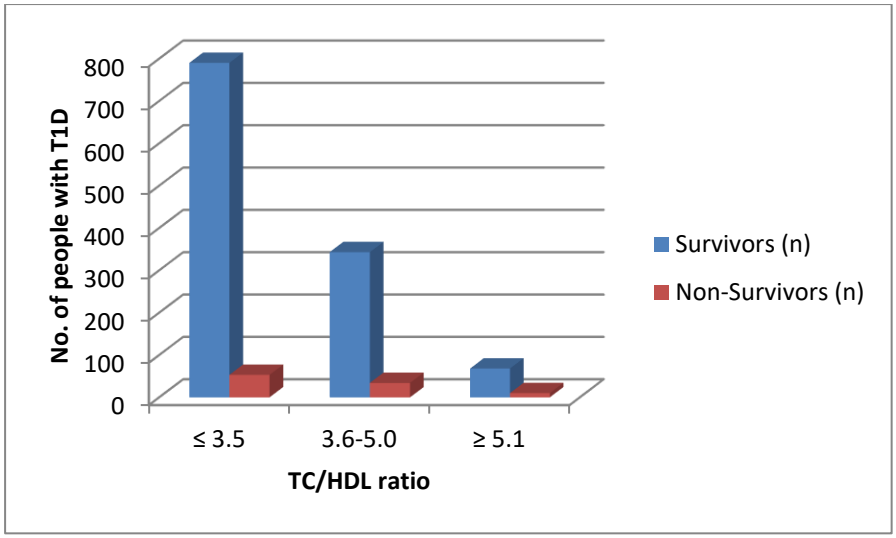


Figure 4.17: Distribution of the survivors and non-survivors with T1D in the Wirral, according to their TC/HDL ratio

4.6.14 Total HDL to LDL ratio

Figure 4.18 shows the distribution of the survivors and non-survivors with T1D in the Wirral, according to their LDL/HDL ratio. Table 4.10 illustrates that 2.2%, 4.7%, and 0.6% of non-survivors had TC/HDL ratios of ≤ 1.5, 1.6-3.6, and ≥ 3.7 respectively.

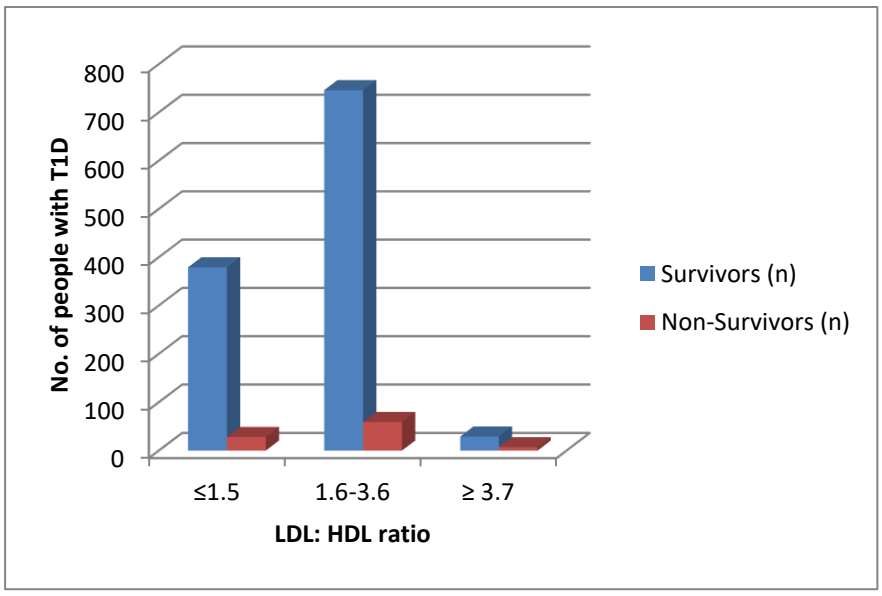


Figure 4.18: Distribution of the survivors and non-survivors with T1D in the Wirral, according to their LDL: HDL ratio

4.6.15 TSH levels (mU/L

Figure 4.19 shows the distribution of the survivors and non-survivors with T1D in the Wirral, according to their LDL: HDL ratio. Table 4.10 shows that the largest cohort of the survivors (82.7%), non-survivors (6.8%), and total T1D (89.5%) had normal TSH levels (0.4-4.0 mU/L). For non-survivors, 0.1% and 1.4% had TSH level of ≤ 0.4 mU/L and ≥ 4.0 mU/L respectively.

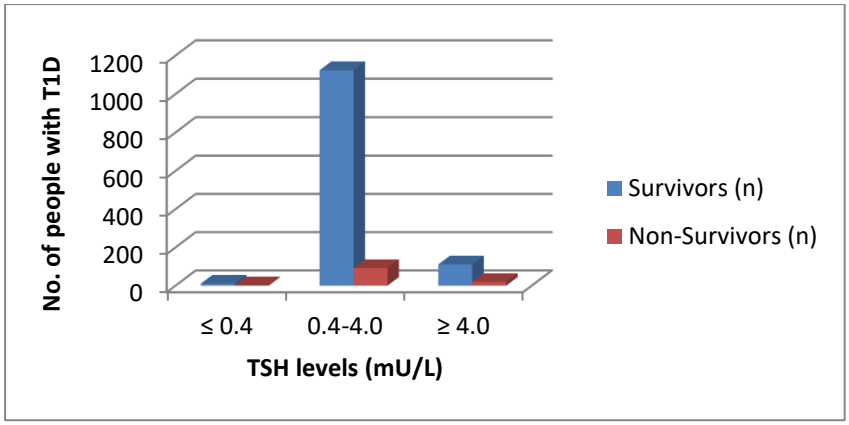


Figure 4.19: Distribution of the survivors and non-survivors with T1D in the Wirral, according to their TSH levels

4.6.16 Calendar year of diagnosis

Table 4.11 illustrates the distribution of amongst survivors, non-survivors, and total T1D population, according to calendar year of diagnosis. Figure 4.20 shows the distribution of the survivors and non-survivors with T1D in the Wirral, according to their calendar year of diagnosis. The subsequent diagnosis of T1D over the 12 years followed a sinusoidal pattern but overall a declining trend from 2.4% in 2000 to 0.5% in 2011. Most of the individuals in this cohort were diagnosed before the year 2000 (65.9%). During the follow up period, the peak period of diagnosis was noticed in the year 2003 (3.3%), however, before this peak, levels of diagnosis were 2.4% in 2000, 2.8% in 2001, 2.8% in 2002 and then a gradual decline over the next three years to 1.8% in 2006. In 2007, there a minor surge in diagnosis to 2.3%, with a further increase in 2008 to 2.7%.

Table 4.11: Distribution of amongst survivors, non-survivors, and total T1D population, according to calendar year of diagnosis including chi square test for statistical significant association between survivors and non-survivor

Characteristics	Survivors N (%)	Non-Survivors N (%)	Total T1DM	p-values
Calendar year of diagnosis				0.005
≤ 1999	965 (65.9)	110 (7.5)	1075 (73.4)	
2000	35 (2.4)	0 (0)	35 (2.4)	
2001	41 (2.8)	0 (0)	41 (2.8)	
2002	39 (2.7)	2 (0.1)	41 (2.8)	
2003	47 (3.2)	2 (0.1)	49 (3.3)	
2004	36 (2.5)	2 (0.1)	38 (2.6)	
2005	34 (2.3)	0 (0)	34 (2.3)	
2006	26 (1.8)	1 (0.1)	27 (1.8)	

2007	33 (2.3)	0 (0)	33 (2.3)	
2008	38 (2.6)	1 (0.1)	39 (2.7)	
2009	20 (1.4)	0 (0)	20 (1.4)	
2010	26 (1.8)	0 (0)	26 (1.8)	
2011	7 (0.5)	0 (0)	7 (0.5)	
Total	1347 (91.9)	118 (8.1)	1465 (100)	

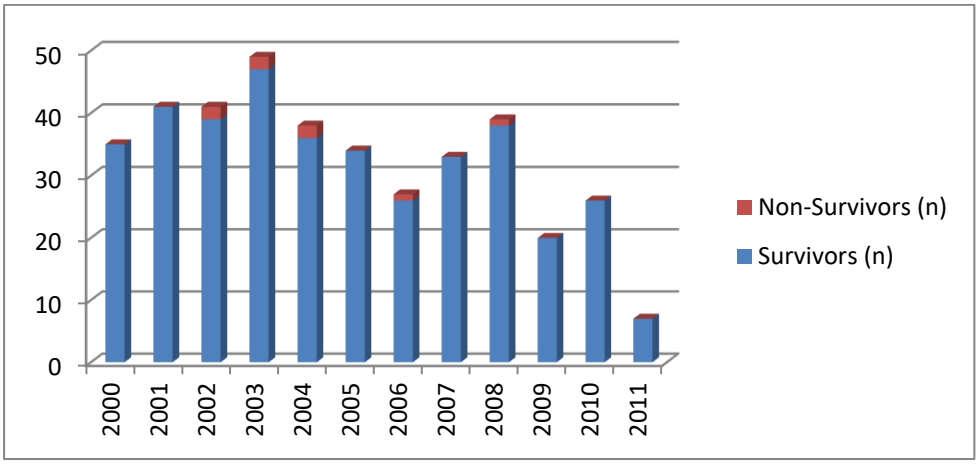


Figure 4.20: Distribution of the survivors and non-survivors with T1D in the Wirral, according to their calendar year of diagnosis

A decline to 1.4% was noted in 2009, and then rise to 1.8% in 2010. The lowest level of diagnosis was recorded in 2011 (0.5%). The largest cohorts of survivors were recorded in 2003 (3.2%), but in the non-survivors group, 3 consecutive years recorded similar proportions of non-survivors, these were 2002 (0.1%), 2003 (0.1%), 2004 (0.1%). Following 2004, there was a decline in the number of non-survivors. The association between survivors and non-survivors considering the calendar of diagnosis was statistically significant (p-value=0.005, df =12, X^2=28.34).

Table 4.12: Year of death, number of deaths and rates of change in non-survivors with T1D in the Wirral

Year of death	**No. of Death**	**Rate of change (%)**
≤ 1999	110	-
2000	0	-
2001	0	-
2002	2	1.79
2003	2	1.75
2004	2	1.72
2005	0	0
2006	1	0.85
2007	0	0
2008	1	0.85
2009	0	0
2010	0	0

2011	0	0

4.7 Cause of mortality

Of the 113 deaths recorded for the cohort that indicated a proportion of 7.75% of the total T1D patients, records for only 37 participants were retrieved. The principal cause of death in this cohort was malignancy-related 8 deaths (21.6%), this was followed by cardiovascular disease and sepsis, each having 6 deaths (16.2%) respectively. Cerebrovascular disease accounted for 5 deaths (13.5%). These four conditions accounted for over 60% of all-cause mortality in this cohort of T1D patients. Death from diabetes complications (hypoglycaemia) was recorded in 1 patient (2.7%). Table 4.13 below further illustrated the cause of mortality in this cohort.

Table 4.13: Cause of mortality

Cause of death	**Males N (%)**	**Females N (%)**	**Total N (%)**	**ICD-10th revision block**
Cardiovascular disease	3 (8.1)	3 (8.1)	6 (16.2)	I00 - I09, I11, I13, I20 - I51, I21 - I22, I71 - I78
Cerebrovascular disease	5 (13.5)		5 (13.5)	I60 - I69
Malignancy related	6 (16.2)	2 (5.4)	8 (21.6)	C00-C97
Renal disease		1 (2.7)	1 (2.7)	N17 - N19
Hepatic and Gastrointestinal	3 (8.1)	1 (2.7)	1 (2.7)	K70, K73 - K74
Sepsis	3 (8.1)	3 (8.1)	6 (16.2)	A40-A41, A00-A09, A20-A39, A42-A49, A54-A99, B00-B19, B25-B99
Respiratory disease		2 (5.4)	2 (5.4)	J40 - J47

Diabetes complications		1 (2.7)	1 (2.7)	E10 - E14
Dementia	2 (2.7)	1 (2.7)	3 (8.1)	G30
Others (obesity, external cause		1 (2.7)	1 (2.7)	V01, V05 - V06, V091, V093 - V099, V10 - V11, V15 - V18, V193, V198 - V199, V800 - V802, V806 - V809, V812 - V819, V822 - V829, V879, V889, V891, V893, V899, V90 - X599, Y85 - Y869
Total	22 (59.5)	15 (40.5)	37 (100)	

4.8 Mortality analysis and competing risk

4.8.1. Age- and sex-specific mortality

Figure 4.21 and Table 4.14 illustrates the Age- and sex-specific mortality rates in both sexes with T1D in the Wirral. This reflects a fluctuating but rising trend with age groups. For both sexes, the age-specific mortality rates were least in the age 0-4 years, in males and females, the age-specific mortality rates were 0.039 (39 deaths per 1000 person-years) and 0.020 (20 deaths per 1000 person-years). In the pre-pubertal age group (10-14 years) there was a reversal of trend with females having higher age-specific mortality (0.072 [72 per 1000 person years]) as compared to males (0.035 [35 per 1000 person-years). In the 15 -19 years age group there was a reversal of trend as males had higher age-specific mortality rates than females. The age-specific mortality rates for the age-group 20-24 year were similar, but the rates in the 25-29 age group were more than doubles for females (0.158 [158 per 1000 person years]) as compared to males (0.056 [56 per 1000 person years]). In the age group, 30-34 years the age-specific mortality rates for males was slightly higher than females 0.1286 (128.6 per 1000) and 0.1176 (117.6 per 1000) respectively. However, in there was a reversal in the trend for the age group 35-39 were females had a marked increase in the age-specific mortality rate than males having values of 0.2727 (272 per 1000) and 0.0746 (74.6 per 1000). This indicates almost a fourfold increase age-specific mortality rate between females and males in this age group. The total observation time was 17,496 person-years with an overall age-specific mortality rate of 0.0775 (77.5 per 1000 person-years). Figure 4.22 Age- and sex-adjusted mortality rates in both sexes with T1D in the Wirral. After initial adjustment, the age-adjusted mortality rates according to gender followed a similar pattern to age-specific mortality rates. The age-adjusted mortality rate was lowest in the age group 0-4 years in both sexes, having age-adjusted mortality rates of 0.0034 (3.4 per 1000 person-years) and 0.0017 (1.7 per 1000 person-years) in males and

females respectively. For males, the age group with the highest age-adjusted mortality rate was in the age group 20-24 years having an age-adjusted mortality rate of 0.0170 (17 per 1000 person-years) followed by age group 15-19 years with an age-adjusted mortality rate of 0.0119 (11.9 per 1000 person-years). In females, the highest recorded age-adjusted mortality rate was in the 25-29 year age group 0.0198 (19.8 per 1000 person-years, followed closely by age group 35-39 with an age-adjusted mortality rate of 0.0187 (18.7 per 1000 person-years).

Table 4.14: Age- and sex-specific, age- and sex-adjusted mortality rates in T1D and the Wirral standard population (per 1000)

Age group	**T1DM population in the Wirral**						**Wirral standard population**		
	Age-specific mortality			**Age-adjusted mortality**			**Standardised Age-adjusted mortality**		
	Males	**Females**	**Total T1D**	**Males**	**Females**	**Total T1D**	**Males**	**Females**	**Total**
0 – 4	0.0395	0.0200	0.0317	0.0034	0.0017	0.0021	0.0050	0.0025	0.0041
5 – 9	0.0442	0.0165	0.0299	0.0071	0.0026	0.0049	0.0053	0.0020	0.0037
10 – 14	0.0351	0.0724	0.0526	0.0078	0.0160	0.0123	0.0045	0.0093	0.0071
15 – 19	0.0952	0.0649	0.0824	0.0119	0.0081	0.0112	0.0129	0.0088	0.0122
20 – 24	0.1204	0.1222	0.1214	0.0170	0.0173	0.0195	0.0147	0.0150	0.0169
25 – 29	0.0561	0.1579	0.0984	0.0070	0.0198	0.0137	0.0068	0.0192	0.0132
30 – 34	0.1286	0.1176	0.1250	0.0092	0.0084	0.0102	0.0149	0.0137	0.0166
35 – 39	0.0746	0.2727	0.1400	0.0051	0.0187	0.0112	0.0095	0.0349	0.0208
Total	0.0698	0.0874	0.0775	0.0698	0.0874	0.0775	0.0698	0.0874	0.0775

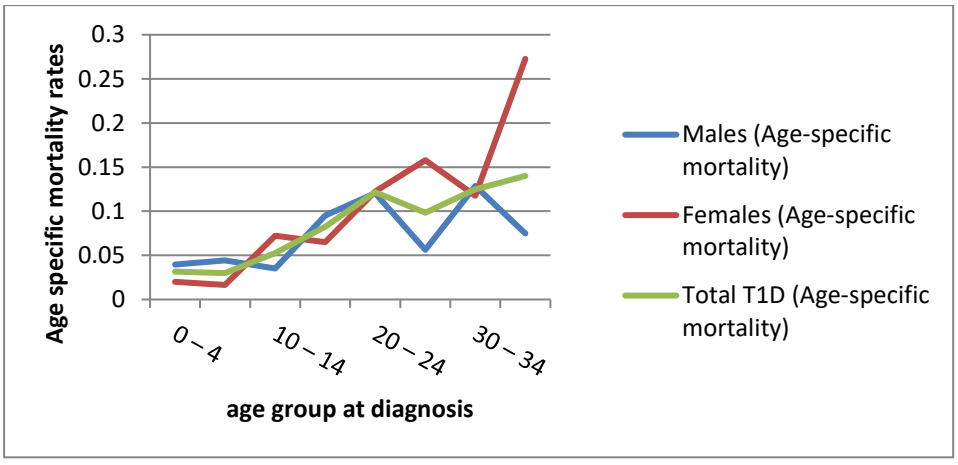


Figure 4.21: Age- and sex-specific mortality rates in both sexes with T1D in the Wirral.

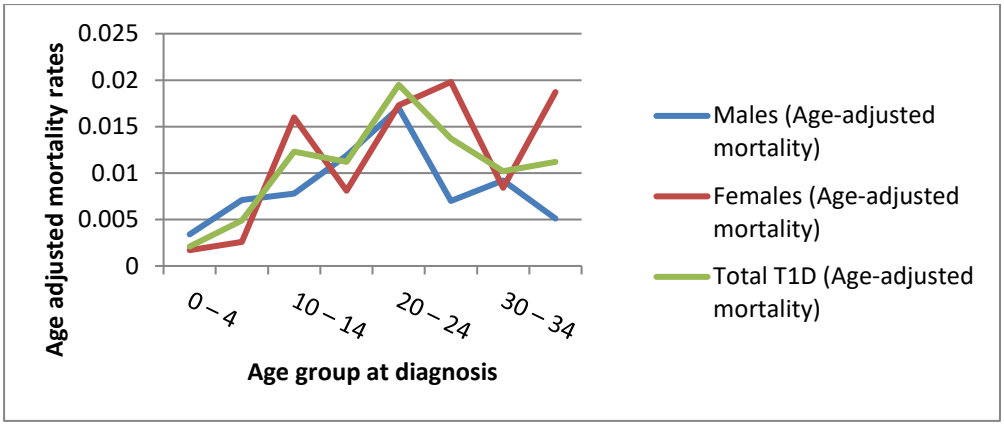


Figure 4.22: Age- and sex-adjusted mortality rates in both sexes with T1D in the Wirral.

Females had higher age-adjusted mortality than males in the following age groups 10-14, 20-24, 25-29, and 35-39. In the 15-19 year age groups, the age-adjusted mortality rate for males was almost 2 times the females' age-adjusted mortality rate, having 0.0119 (11.9 per 1000 person-years) and 0.0081 (8.1 per 1000 person-years) respectively.

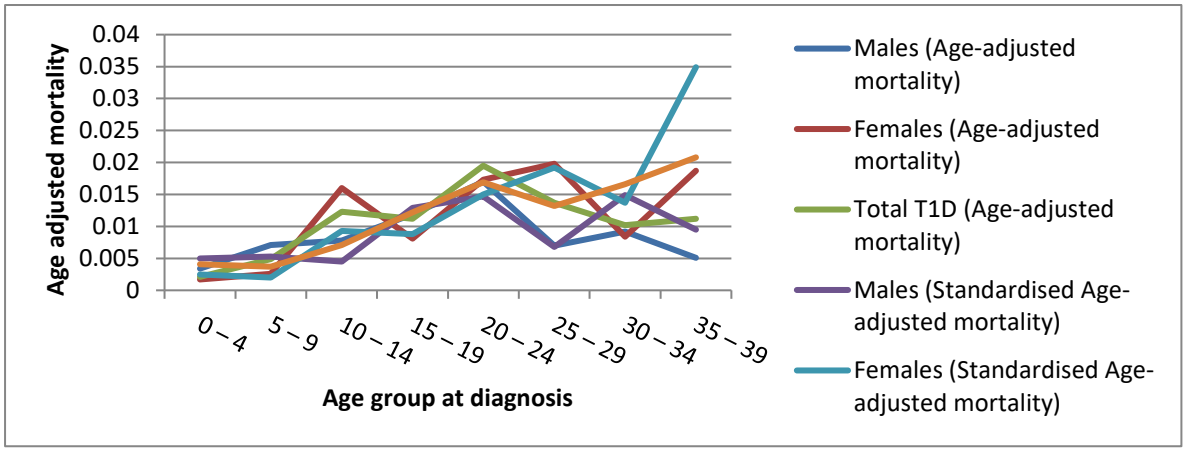


Figure 4.23: Age- and sex-adjusted mortality rates compared to Standardised to Age- and sex-adjusted mortality rates in both sexes with T1D in the Wirral.

Figure 4.23 reflects standardised Age- and sex-adjusted mortality rates in both sexes with T1D in the Wirral. This was then standardised to the local Wirral population. A comparison between the Age- and sex-adjusted mortality rates and the standardised to Age- and sex-adjusted mortality rates reflected a sinusoidal pattern but gradually rising trend. The age groups with the highest standardised age-adjusted mortality rates were 30-34 (0.0149 [14.9 per 1000 person years]) in males and 35-39 (0.0349 [34.9 per 1000 person years]) in females. Predominantly, males had higher standardised age-adjusted mortality rates in the following four age groups, 0-4, 5-9, 15-19, and 30-34.

Figure 4.24 shows age- and sex-specific mortality rates compared to age- and sex-adjusted mortality rates in both sexes with T1D in the Wirral. While the age- and sex-specific mortality rates for a sinusoidal pattern, the age-adjusted mortality rates follow a linear trend.

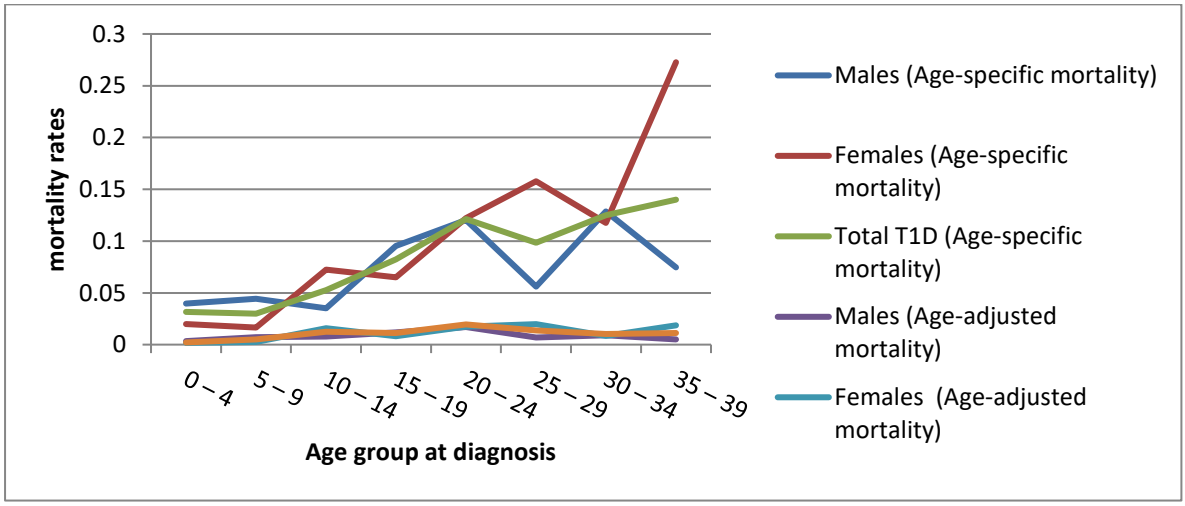


Figure 4.24: Age- and sex-specific mortality rates compared to the age- and sex-adjusted mortality in T1D in the Wirral

Table 4.15 shows a comparison of the age- and sex-specific rate difference, rate ratio and percentage change in adjusted and specific mortality rates in T1D in the Wirral. The mortality rate ratios were higher in males than females in three age groups 5-9, 30-34 and 35-39 years. For the females, the rate ratios followed a sinusoidal pattern with the highest rate ratio in the age group 35-39 years. The male cohort showed a similar sinusoidal pattern with the highest rate ratio also in the age group 35-39 years.

Table 4.15: Age- and sex-specific rate difference, rate ratio and percentage change in adjusted and specific mortality rates in T1D in the Wirral.

Age group	Mortality rate difference		Mortality rate ratio		Mortality rate per cent change (%)	
	Males	Females	Males	Females	Males	Females
0 – 4	-0.0012	-0.0006	0.67	0.67	47.1	47.1
5 – 9	-0.0048	--0.0018	0.35	0.33	-25.4	-23.1
10 – 14	-0.0060	-0.0127	0.26	0.27	42.3	-41.9
15 – 19	-0.0065	-0.0043	0.50	0.51	8.4	8.6
20 – 24	-0.0167	-0.0119	0.13	0.40	-13.5	-13.3
25 – 29	-0.0042	-0.0130	0.44	0.45	-2.9	3.0
30 – 34	-0.0027	-0.0024	0.74	0.11	62.0	63.1
35 – 39	-0.0007	-0.0036	0.87	0.86	86.3	86.6

Considering mortality rate difference, for males, there was a gradual initial increase in the rate difference up to the 20-24 age groups, and then a gradual decline onwards to the age group 35-39 years. Conversely, females a more varying pattern for mortality rate difference. The mortality rates per cent change were almost similar in both groups. Before the year 2000, the mortality rate ratio was similar for males and females respectively 0.11 for both genders. Considering the period 2000 to 2012, the highest risk ratio was in 2006 for females (4.40) and 2004 for males (3.07).

Table 4.16: Calendar year- and sex-specific rate difference, rate ratio and percentage change in adjusted mortality rates, and absolute excess risk in T1D in the Wirral

Calendar year	Mortality rate difference		Mortality rate ratio		Mortality rate change (%)	
	Males	Females	Males	Females	Males	Females
≤1999	-0.0647	-0.0683	0.11	0.11	-89.0	-89.0
2000	-	-	-	-	-	-
2001	-	-	-	-	-	-
2002	0.0023	0.0027	2.77	2.80	176.9	180.0
2003	-	0.0052	-	2.41	-	140.5
2004	-	0.0060	-	3.07	-	206.9
2005	-	-	-	-	-	-
2006	0.0034	-	4.40	-	340	-
2007	-	-	-	-	-	-
2008	-	0.0033	-	2.94	-	194.1
2009	-	-	-	-	-	-
2010	-	-	-	-	-	-
2011	-	-	-	-	-	-

4.8.2. Age-, sex-specific and Age-, sex-adjusted mortality rates, according to calendar-year

Age-, sex- and calendar-year adjusted mortality rates are illustrated in table 4.17. Considering the period between 2000 and 2012, the maximal specific mortality rates for this cohort occurred in 2004 having a specific mortality rate of 0.0526 (52 per 1000 person-years). Considering gender differentiation, males and females had their maximal specific mortality rates in 2006, 0.0556 (55.6 per 1000 person-years), and 2004, 0.1111 (111 per 1000) respectively. The total T1D population had an overall specific mortality rate of 0.0.0805 (80.5 per 1000 person-years). By gender differentiation, the specific mortality rate by calendar year followed a sinusoidal pattern. Females had higher specific mortality rates than males in all years except. The total T1D population also followed a similar sinusoidal pattern. After adjustment and standardisation to the Wirral population, the adjusted mortality rate for this cohort had minimal variations, while the standardised adjusted mortality rates showed a sinusoidal pattern.

Table 4.17: Calendar year- and sex-specific and calendar year- and sex-adjusted mortality rates in T1D and the Wirral standard population

Calendar year	Wirral T1D specific mortality rate			Wirral adjusted mortality rate T1D			Standardised Wirral adjusted mortality rate		
	Males	Females	Total T1D	Males	Females	Total T1D	Males	Females	Total T1D
≤1999	0.1005	0.1045	0.1023	0.0727	0.0767	0.0751	0.0080	0.0084	0.0082
2000	-	-	-	-	-	-	-	-	-
2001	-	-	-	-	-	-	-	-	-
2002	0.0455	0.0526	0.0488	0.0013	0.0015	0.0014	0.0036	0.0042	0.0039
2003	-	0.1111	0.0408	-	0.0037	0.0014	-	0.0089	0.0033
2004	-	0.1111	0.0526	-	0.0029	0.0014	-	0.0089	0.0042
2005	-	-	-	-	-	-	-	-	-
2006	0.0556	-	0.0370	0.0010	-	0.0007	0.0044	-	0.0030
2007	-	-	-	-	-	-	-	-	-
2008	-	0.0625	0.0256	-	0.0017	0.0007	-	0.0050	0.0020
2009	-	-	-	-	-	-	-	-	-
2010	-	-	-	-	-	-	-	-	-
2011	-	-	-	-	-	-	-	-	-
Total	0.0741	0.0888	0.0805	0.0741	0.0888	0.0805	0.0741	0.0888	0.0805

4.8.3. Standardised mortality ratio (SMR)

Standardized Mortality Ratio (SMR) is defined as the ratio between the observed numbers of deaths to the number of deaths that would be expected in a study population expressed as a comparison to the Wirral standard population (per 1000).

Table 4.18: Age- and sex-specific SMR with their corresponding 95% CI in T1D in the Wirral

Age group	SMR (95% CI)		
	Males	Females	Total
0 – 4	7.89 [(-1.28) – 17.06]	8 [(-7.7) – 15.7]	7.96 [0.15 – 15.23]
5 – 9	8.33 [1.02 – 15.64]	8.26 [(-3.1) – 19.4]	8.05 [2.07 -14.03]
10 – 14	7.79 [1.56 – 14.02]	7.76 [3.9 – 11.6]	7.42 [3.95 – 10.89]
15 – 19	7.41 [2.82 – 12]	7.37 [(-0.4) -15.17]	6.76 [3.35 – 10.17]
20 – 24	8.18 [3.73 – 11.91]	8.16 [4.34 – 11.94]	7.18 [4.36 – 10]
25 – 29	8.22 [1.63 – 14.81]	8.21 [3.56 – 12.86]	7.43 [4 – 10.86]
30 – 34	8.65 [3.01 – 14.29]	8.51 [0.16 -16.86]	7.51 [3.41 – 11.61]
35 – 39	7.81 [0.95 – 14.67]	7.83 [2.71 – 12.95]	6.73 [3.2 – 10.26]
Total	1 [0.96 – 1.04]	1 [0.96 -1.04]	1 [0.96 -1.04]

The respective distribution of age- and sex-specific SMRs including their corresponding 95% CI in the total T1D population, males and females respectively are reflected in Figures 4.25 4.26, and 4.27. The highest SMRs for both sexes was recorded in the age group 30-34 having SMRs of 8.65 [95% CI: 3.01 – 14.29], 8.51 [95 % CI: 0.16 -16.86] in males and females respectively. The highest value for SMR in total T1D population was 8.05 [95% CI: 2.07 - 14.03] in the age group 5-9 years. The broadened CI reflect that the exact value for the SMR remains uncertain, this is due to the influence of the effect sizes in the age groups. Males had higher SMRs than females for all but three age groups 0-4, 5-9, and 35-39 years.

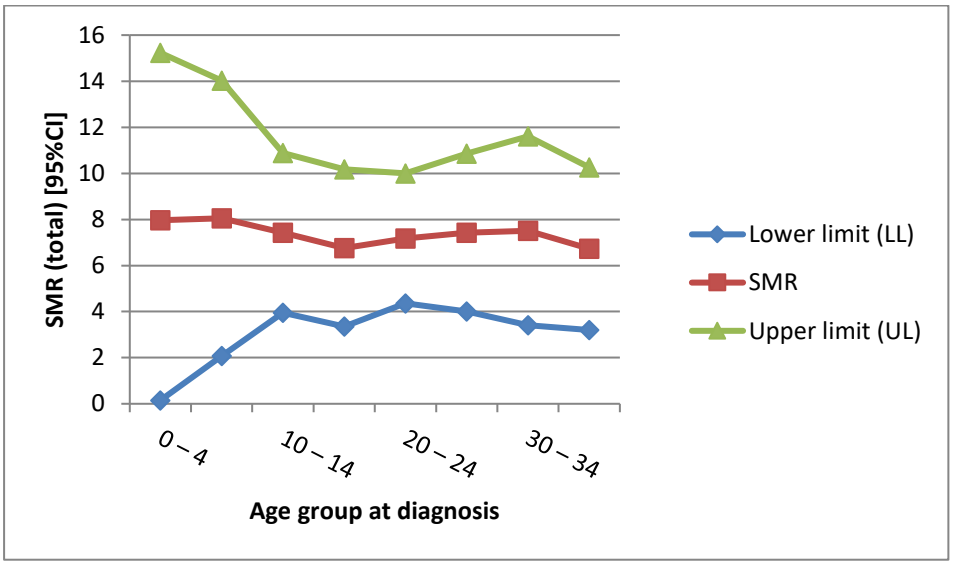


Figure 4.25: Age- and sex-specific SMR [95%CI] in total T1D population

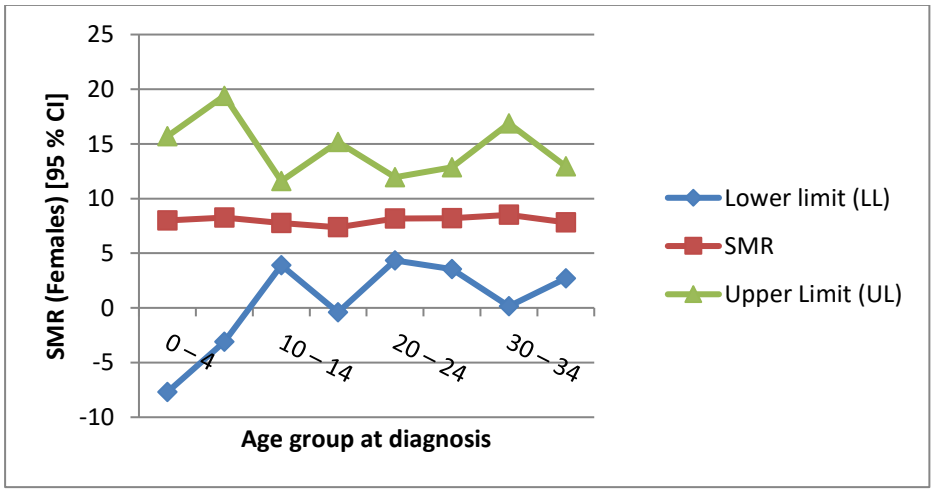


Figure 4.26: Age- and sex-specific SMR [95% CI] in females

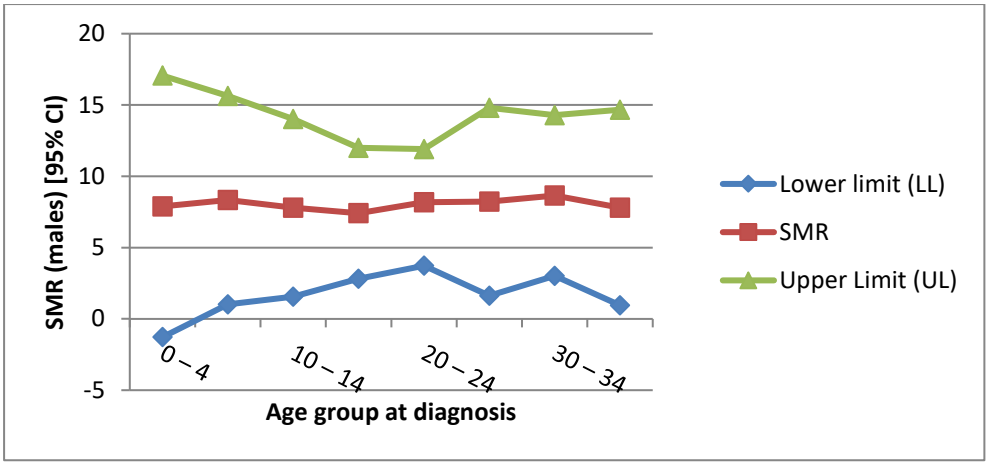


Figure 4.27: Age- and sex-specific SMR [95% CI] in males

Table 4.19 reflects the SMRs according to the calendar year of diagnosis. The overall trend reflects no change SMR within the follow-up period. There were no deduced values for SMRs in the years 2000, 2001, 2005, 2007, 2009, 2010, 2011. This was because they estimated zero person-years. These values can be attributed to the small numbers in this cohort. Further illustration is reflected in Figure 4.28. There were no variations in SMRs according to gender reflected in Figures 4.29 and 4.30.

Table 4.19: Calendar year SMR [95%CI] in T1D in the Wirral

Calendar year	**SMR [95% CI]**		
	Males	**Females**	**Total**
≤1999	12.6 [(-2.5) – 27.7]	12.4 [4.95 – 19.85]	12.5 [10.2 -14.8]
2000		-	-
2001		-	-
2002	12.5 [(-12) – 37]	12.5 [(-12) – 37]	12.5 [(-4.8) – 29.8]
2003		12.5 [(-4.8) – 29.8]	12.5 [(-4.8) – 29.8]
2004		12.5 [(-4.8) – 29.8]	12.5 [(-4.8) – 29.8]
2005		-	-
2006	12.5 [(-12) – 37]	-	12.5 [(-12) – 37]
2007		-	-
2008		12.5 [(-12) – 37]	12.5 [(-12) – 37]
2009		-	-

2010		-	-
2011		-	-
Total	1 [0.74 – 1.26]	1 [0.96 – 1.04]	1 [0.82 – 1.18]]

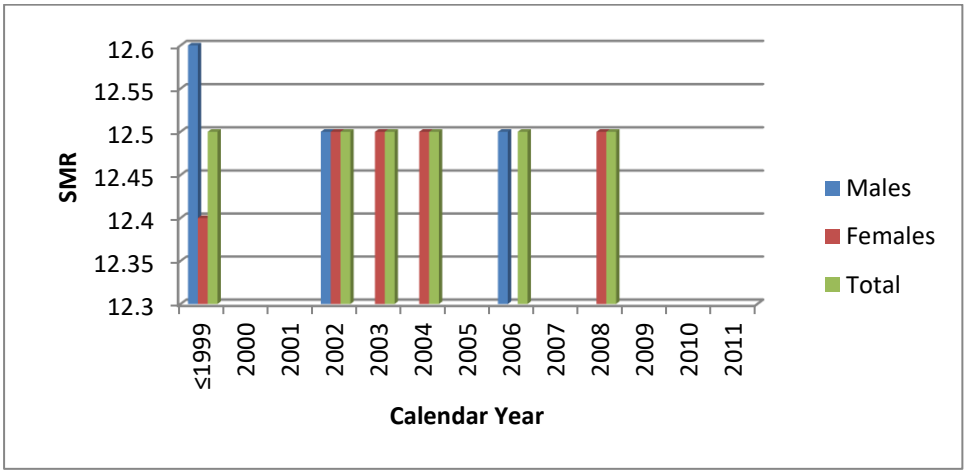


Figure 4.28: SMR per calendar- year in people with T1D

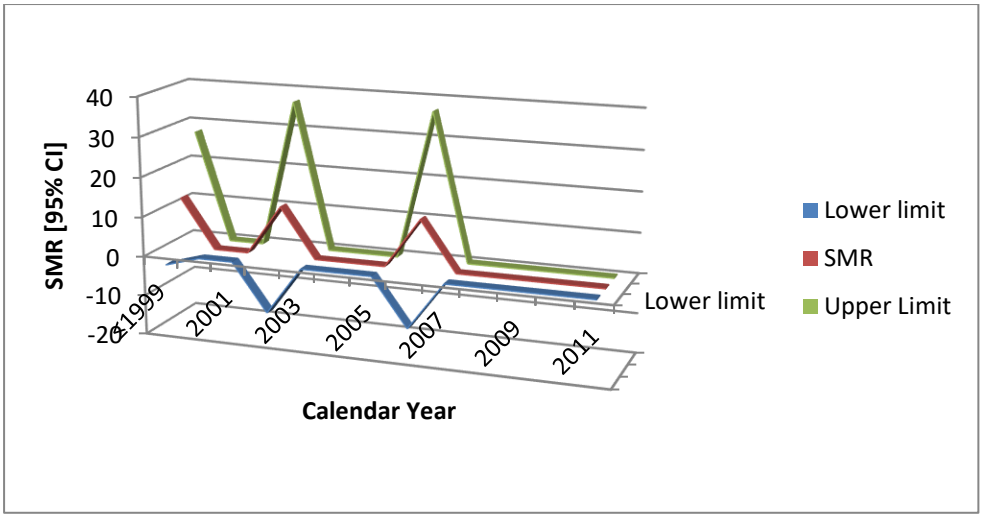


Figure 4.29: SMR [95%CI] according to calendar year in males with T1D in the Wirral

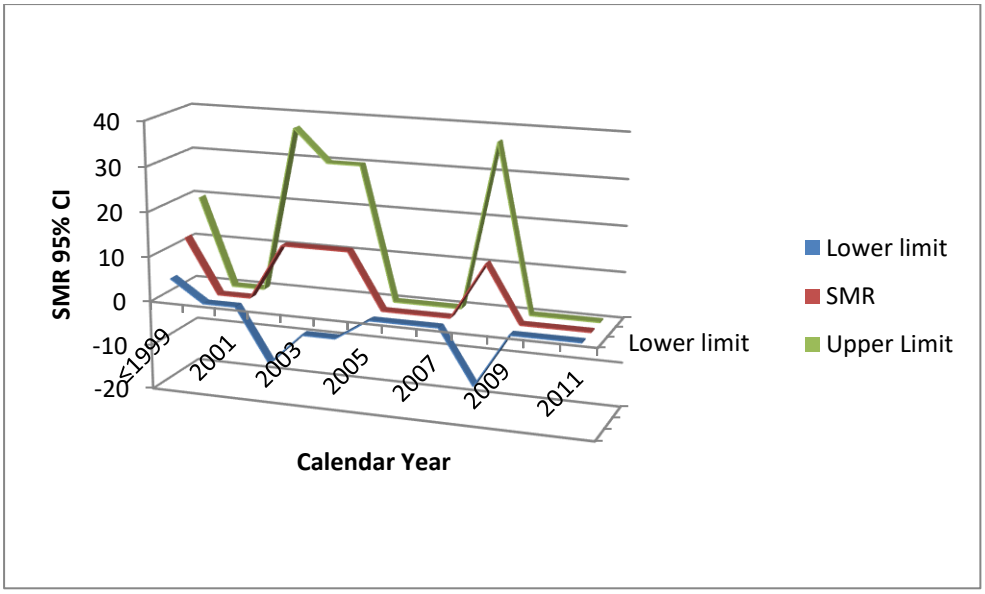


Figure 4.30: SMR [95% CI] according to the calendar year in females with T1D in the Wirral

4.9 Median survival

Median survival in this population subset (T1D population), relates to a statistical measure that determines how long patients survive with disease in general, estimated in years. Table 4.20 reflects estimates of comparative measures of the median survival times in years for the T1D population, using the predictors of mortality and estimating the p-values for males and females. Analysis of the median survival showed that significant predictors (p-value <0.05) of survival for this cohort were duration of diabetes, HbA_{1c}, Serum creatinine, BMI, and lipid levels.

4.9.1. Gender and survival time

The overall median survival time for T1D population was 76.906 years [95% CI: 75.041 – 78. 771]. Males had a median survival period of 77.185 years [75.191 – 79.179], which was slightly higher than females with median survival of 76.011 years [73.169 – 78.000]. Figure 4.31 illustrates the survival curve according to gender in people with T1D in the Wirral, the relationship between both sexes was not statistically significant (p-value= 0.226).

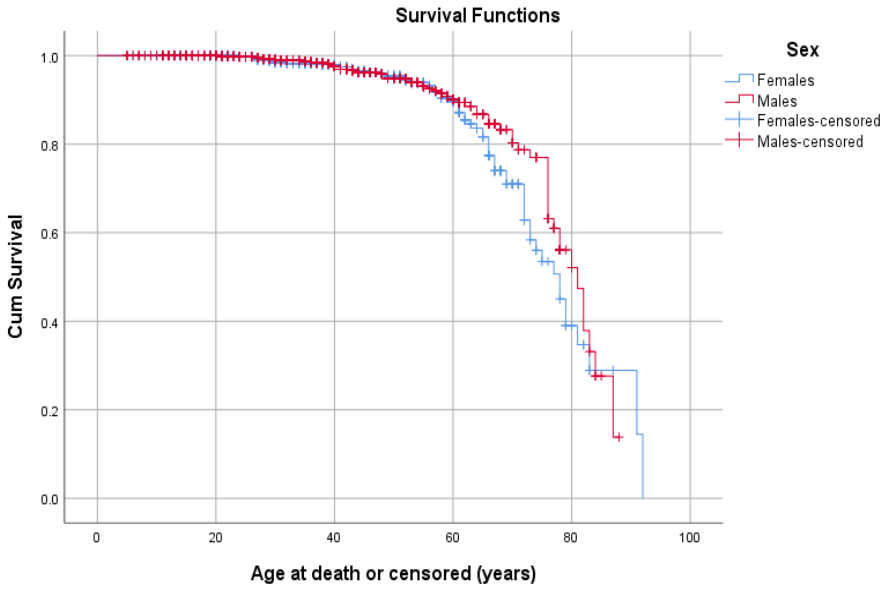


Figure 4.31: Survival curve according to gender in people with T1D in the Wirral

Table 4.20: Comparative median survival of the various predictors of mortality in T1D including p-values from log-rank test for statistical significance

Predictors of mortality	**Median survival (years)**			**P-values**
	Males [95%CI]	**Females [95%CI]**	**Total [95% CI]**	
Gender	77.185 [75.191 – 79.179]	76.011 [73.169 – 78.000]	76.906 [75.041 – 78. 771]	0.226
Age of diagnosis (years)				0.625
0 – 4	62.115 [56.308 – 67.922]	63.348 [60.181 – 66.515]	62.980 [59.151 – 66.810]	
5 – 9	69.973 [64.633 – 75.313]	68.550 [65.036 – 72.063]	71.626 [68.197 – 75.055]	
10 – 14	71.423 [65.729 – 77.117]	73.948 [65.882 – 82.013]	75.513 [68.989 – 82.037]	
15 – 19	73.058 [68.965 – 77.150]	72.917 [66.767 – 77.626]	72.923 [69.751 – 76.096]	
20 – 24	76.318 [72.826 – 79.809]	72.947 [69.579 – 76.315]	75.328 [72.612 – 78.043]	
25 – 29	77.576 [73.550 – 81.603]	76.309 [71.682 – 80.935]	77.527 [74.099 – 80.955]	
30 – 34	78.799 [73.942 – 83.655]	68.656 [64.728 – 72.584]	77.586 [73.117 – 82.054]	
35 – 39	81.893 [76.921 – 86.866]	75.729 [67.229 – 84.228]	79.223 [74.079 – 84.366]	
Total	77.192 [75.075 – 79.309]	76.634 [73.505 – 79.762]	77.228 [75.191 – 79.265]	
Duration of Diabetes				0.004
1-10	48.416 [47.625 – 49.207]	45.527 [42.961 – 48.094]	47.396 [46.334 – 48.457]	
11-20	72.781 [70.370 – 75.193]	55.189 [53.635 – 56.744]	72.168 [69.729 – 74.607]	
21-30	65.918 [64.402 – 67.433]	73.792 [68.679 – 78.904]	75.221 [72.891 – 77.551]	
31-40	77.667 [75.847 – 79.487]	68.555 [66.423 – 70.687]	74.279 [70.933 – 77.626]	
41-50	78.276 [73.993 – 82.559]	76.666 [72.746 – 80.586]	78.677 [75.427 – 81.928]	
Total	79.020 [76.058 – 81.982]	73.434 [72.746 – 80.586]	76.936 [74.358 – 79.514]	
Index of Multiple Deprivation				0.607
Quintile 1(most deprived)	76.109 [72.251 – 79.968]	73.820 [68.684 – 78.957]	75.490 [72.050 – 78.929]	

Quintile 2(above average)	76.678 [70.274 – 83.081]	80.179 [74.081 – 86.277]	79.409 [74.452 – 84.367]	
Quintile 3(average)	78.940 [74.958 – 82.922]	77.483 [73.773 – 81.193]	78.004 [74.999 – 81.010]	
Quintile 4(below average)	77.910 [75.068 – 80.753]	70.117 [66.389 – 73.845]	74.356 [71.895 – 76.817]	
Quintile 5 (least deprived)	76.796 [73.188 – 80.404]	78.065 [72.537 – 83.594]	77.099 [73.755 – 80.422]	
Total	77.185 [75.191 – 79.179]	76.011 [73.169 – 78.854]	76.906 [75.041 – 78.771]	
HbA1c %(mmol/mol)				0.034
≤ 5.9 (41)	59.415 [44.180 - 79.649]	58.286 [45.040 - 93.531]	59.101 [45.607 – 72.595]	
6.0-6.4(42-46)	77.873 [72.679 - 83.066]	80.000 [67.005 - 85.928]	82.478 [77.644 – 87.312]	
6.5-6.9(48-52)	73.000 [71.573 - 90.427]	74.000 [76.272 - 91.728]	72.931 [68.394 – 77.469]	
7.0-7.4(53-57)	79.600 [77.009 - 86.191]	73.379 [67.106 - 79.652]	76.595 [69.380 – 83.810]	
7.5-8.0(58-64)	77.000 [74.023 - 85.977]	75.000 [70.214 - 95.786]	76.633 [73.697 – 79.569]	
8.1-8.4(65-68)	78.000 [70.383 - 85.617]	75.000 [71.554 - 92.446]	77.815 [72.236 – 83.394]	
8.5-9.0(69-75)	82.000 [80.519 - 83.481]	78.000 [72.051 - 83.949]	77.214 [74.726 – 79.703]	
9.1-9.4(76-79)	74.000 [62.585 - 85.415]	78.254 [71.696 - 84.813]	68.493 [64.895 – 72.092]	
9.5-10(80-86)	81.000 [71.930 - 96.070]	78.000 [67.630 - 88.370]	74.913 [70.375 – 79.451]	
≥ 10.1	71.000 [67.020 - 74.980]	75.217 [70.903 - 79.531]	73.620 [69.727 – 77.512]	
Total	75.000 [75.777 - 84.223]	77.000 [77.122 - 82.878]	76.542 [74.508 – 78.576]	
Smoking status				0.382
Never smoked	77.750 [75.341 – 80.159]	77.768 [74.018 – 81.519]	78.518 [75.634 – 81.401]	
Smokes	75.338 [71.689 – 78.987]	69.159 [62.732 – 75.589]	73.104 [69.584 – 76.625]	
Ex-smoker	76.339 [75.192 – 81.459]	73.580 [69.910 – 77.251]	77.223 [74.557 – 79.889]	
Total	78.617 [76.491 – 80.743]	76.802 [73.706 – 79.899]	78.121 [76.025 – 80.216]	
BMI (kg/m2)				0.023
≤ 18.4	77.000 [76.282 - 85.718]	78.000 [75.000 - 82.000]	77.667 [72.533 - 86.800]	
18.5 - 24.9	68.000 [52.177 - 83.823]	66.000 [55.451 - 76.549]	67.000 [52.282 - 85.718]	
25.0 - 29.9	64.000 [57.337 - 70.663]	69.000 [64.836 - 73.164]	79.000 [78.801 - 85.199]	
30.0 - 34.9	70.000 [67.078 - 72.922]	69.000 [57.313 - 80.687]	78.000 [76.069 - 95.931]	
35.0 - 39.9	40.000 [22.396 - 57.604]	61.000 [48.998 - 73.002]	60.000 [45.075 - 79.925]	
≥ 40	-	59.000 [33.520 - 84.480]	66.000 [63.390 - 75.883]	
Total	68.000 [62.534 - 73.466]	69.000 [65.102 - 72.898]	73.000 [65.562 - 84.438]	
Serum creatinine (µmol/l)				<0.001
< 61	65.500 [63.421 – 67.579]	51.400 [49.912 – 52.888]	60.250[54.128 – 66.372]	
62-106	78.723 [75.711 – 81.735]	77.991 [74.287 – 81.695]	78.522 [75.763 – 81.281]	
107-129	78.889 [75.090 – 82.688]	79.679 [72.013 – 87.344]	79.734 [75.687 – 83.782]	
130-149	73.000 [61.440 – 74.470]	74.133 [66.147 – 82.210]	73.472 [68.134 – 78.810]	
≥ 150	67.955 [61.440 – 74.470]	64.756 [57.052 – 72.461]	66.462 [61.569 – 71.354]	
Total	77.108 [75.059 – 78.930]	76.453 [73.498 – 79.409]	76.995 [75.060 – 78.930]	
Systolic BP (mmHg)				0.687
≤ 99	-	-	-	
100 – 119	57.000 [13.374 - 100.626]	57.000 [33.626 - 80.374]	57.000 [41.443 - 72.557]	
120 – 139	59.000 [50.412 - 67.588]	66.000 [61.003 - 70.997]	65.000 [61.859 - 68.141]	
140 – 159	76.000 [74.243 - 77.757]	73.000 [67.325 - 78.675]	73.000 [70.106 - 75.894]	
≥160	71.000 [61.703 - 80.297]	67.000 [57.947 - 76.053]	70.000 [65.403 - 74.597]	
Total	70.000 [64.781 - 75.219]	69.000 [64.937 - 73.063]	69.000 [65.329 - 72.671]	

Diastolic BP (mmHg)				0.008
≤59	87.000 [87.000 – 87.000]	76.000 [70.120 – 81.880]	79.000 [69.398 – 88.602]	
60-69	76.167 [71.838 – 80.496]	74.100 [70.221 – 77.980]	76.000 [74.091 – 77.909]	
70 – 79	79.741 [76.762 – 82.719]	79.130 [74.446 – 83.814]	82.000 [78.688 – 85.312]	
80 – 89	75.785 [72.954 – 78.616]	72.353 [68.716 – 75.990]	78.000 [76.111 – 79.289]	
90- 99	71.320 [67.124 – 75.516]	63.500 [57.400 – 69.600]	71.000 [66.756 – 75.244]	
≥100	46.667 [38.132 – 55.202]	65.000 [60.842 – 69.158]	62.000 [24.207 – 99.793]	
Total	77.806 [75.493 – 79.452]	76.225 [73.245 – 79.206]	79.000 [76.284 – 81.716]	
Total Cholesterol (mmol/l)				0.002
≤3.9	78.067 [72.011 – 84.122]	68.244 [63.272 – 73.215]	76.000 [71.184 – 81.844]	
4.0-4.5	75.231 [72.073 – 78.390]	74.629 [70.364 – 78.895]	82.000 [76.565 – 87.435]	
4.6-5.2	79.269 [76.907 – 81.631]	75.312 [71.735 – 78.889]	79.000 [71.523 – 86.477]	
5.3-6.1	75.643 [69.501 – 81.784]	74.647 [68.839 – 79.355]	70.000 [63.128 – 76.872]	
≥6.2	64.239 [58.415 – 70.063]	69.812 [62.839 – 76.785]	79.000 [75.895 – 82.105]	
Total	77.191 [74.962 – 79.412]	76.062 [72.941 – 79.184]		
High density lipoproteins [HDL] (mmol/l)				<0.001
0.4-0.7	69.000 [58.043 - 79.957]	73.000 [62.837 - 83.163]	71.000 [62.000 - 86.000]	
0.8-1.1	74.000 [53.808 - 94.192]	65.000 [59.814 - 70.186]	70.000 [59.010 - 82.990]	
1.2-1.5	64.000 [46.937 - 81.063]	67.000 [63.477 - 70.523]	65.000 [44.929 - 85.071]	
≥ 1.6	69.000 [62.195 - 75.805]	67.000 [63.675 - 70.325]	68.000 [62.045 - 89.955]	
Total	-	-	-	
Triglycerides [TG] (mmol/l)				<0.001
≤ 1.6	81.000 [78.152 – 83.848]	78.000 [71.840 – 84.160]	81.000 [77.007 – 84.993]	
1.7-2.2	77.000 [65.451 – 88.848]	74.000 [65.068 – 82.932]	77.000 [73.955 – 80.045]	
≥ 2.3	70.000 [60.933 – 79.067]	72.000 [62.015 – 81.985]	70.000 [64.220 – 75.780]	
Total	81.000 [77.898 – 74.102]	77.000 [71.319 – 82.681]	79.000 [76.061 – 81.939]	
Low density lipoprotein [LDL] (mmol/l)				<0.001
≤ 2.5	81.044 [77.745 – 84.343]	74.994 [71.905 – 78.083]	79.417 [76.711 – 82.063]	
2.6 - 3.3	78.738 [75.829 – 81.647]	79.054 [73.373 – 84.735]	82.000 [77.077 – 86.923]	
3.4 - 4.1	78.145 [73.426 – 82.864]	72.735 [67.902 – 77.568]	78.000 [76.550 – 79.450]	
4.2 - 4.9	49.857 [47.783 – 51.931]	58.857 [50.061 – 67.653]	58.857 [51.547 – 66.167]	
≥ 5.0	45.000 [37.031 – 52.969]	70.800 [45.512 – 96.088]	67.563 [52.433 – 82.692]	
Total	79.512 [77.262 – 81.762]	76.804 [73.703 – 79.906]	78.611 [76.424 – 80.797]	
Total Cholesterol : HDL ratio				<0.001
≤ 3.5	82.000 [79.317 – 84.683]	78.000 [73.539 – 82.461]	81.000 [77.205 – 84.795]	
3.6-5.0	77.000 [72.142 – 81.858]	74.000 [64.528 – 83.472]	77.000 [73.327 – 80.673]	
≥ 5.1	58.000 [49.826 – 66.174]	73.000 [61.078 – 75.783]	70.000 [52.128 – 87.872]	
Total	81.000 [79.101 – 82.899]	78.000 [74.228 – 81.772]	79.000 [76.698 – 81.302]	
Low Density Lipoproteins : HDL ratio				<0.001

≤ 1.5	81.000 [76.755 – 85.245]	77.000 [71.768 – 82.232]	80.808 [76.929 – 84.688]	
1.6-3.6	61.141 [53.151 – 69.670]	78.000 [70.058 – 85.942]	76.030 [73.974 – 78.086]	
≥ 3.7	81.000 [78.213 – 83.783]	73.000 [51.093 – 82.621]	63.823 [57.075 – 70.571]	
Total	79.000 [76.681 – 81.313]	77.000 [72.648 – 81.352]	77.750 [75.571 – 79.930]	

4.9.2. Age at diagnosis and survival time

Table 4.20 highlights that early age at diagnosis (≤ 10 years) accounted for reduced median survival time, in males and females. The overall trend for the total T1D cohort follows a sinusoidal pattern but with a gradually increasing trend. The lowest median survival time from diagnosis was found in the age group 0-4 years while highest median survival time was found in the age group 35-39 years. The overall median survival for the T1D population was 77.228 years [95% CI: 75.191 – 79.265], females 76.634 years [95% CI: 73.505 – 79.762], and males 77.192 years [95% CI: 75.075 – 79.309]. For the total T1D population, there was a gradual increased up the age 10-14 years then a minor drop in age 15-19 years, then a gradual increase up to the age 35-39 years. For diagnosis at the pubertal years (10-14 years), females fared better than males having a median survival time of 73.948 years [95 % CI: 65.882 – 82.013] as compared to 71.423 years [95% CI: 65.729 – 77.117]. The general trend shows that males had better survival in the following age groups 5-9, 15-19, 20-24, 25-29, 30-34, and 35-39 years. Females had better survival if they were diagnosed in the following age groups 0-4, and 10-14 years. There was a marked difference in median survival time of almost 10 years between males and females in the age group 30-34 years, having median survival times of 78.799 years [95% CI: 73.942 – 83.655] and 68.656 years [95% CI: 64.728 – 72.584] respectively. This difference dropped to 6 years in the age group 35-39 year, having median survival periods of 81.893 years [95% CI:76.921 – 86.866], and 75.729 years [95% CI: 67.229 – 84.228] in males and females respectively.

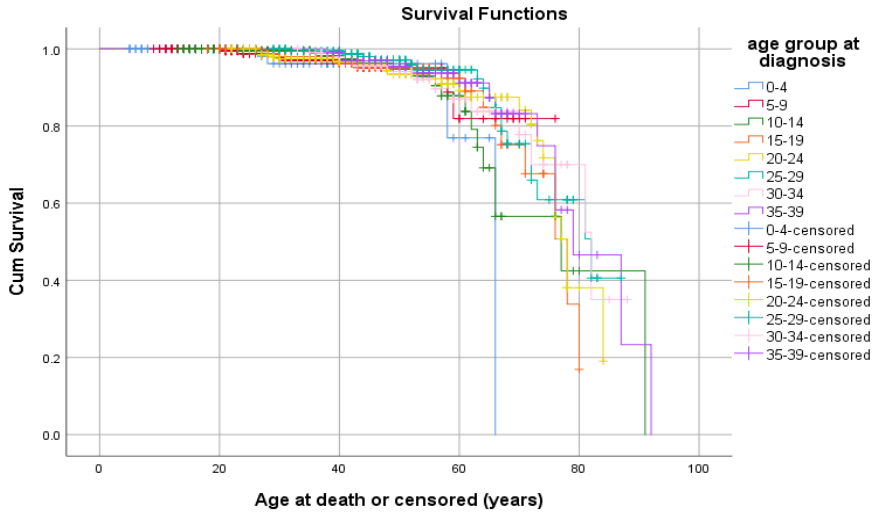


Figure 4.32: Survival curve according to the age at diagnosis (years) in people with T1D

Figure 4.32 shows the survival curve according to the age at diagnosis (years) in people with T1D. The relationship between the groups was not statistically significant (p-value= 0.625).

4.9.3. Duration of diabetes and survival time

Figure 4.33 shows the survival curve according to the duration of diabetes (years) in people with T1D in the Wirral. According to the duration of diabetes, the optimum median survival time was noted to be in those who had duration of diabetes between 41-50 years, 78.276 years [95% CI: 73.993 – 82.559] for males, females 76.666 years [95% CI: 72.746 – 80.586], and overall T1D population 78.677 years [95% CI: 75.427 – 81.928]. The overall values for median survival according to the duration of diabetes was 79.020 years [95% CI: 76.058 – 81.982] in males, 73.434 years [95% CI: 72.746 – 80.586] in females, and 76.936 years [95% CI: 74.358 – 79.514] in the total population

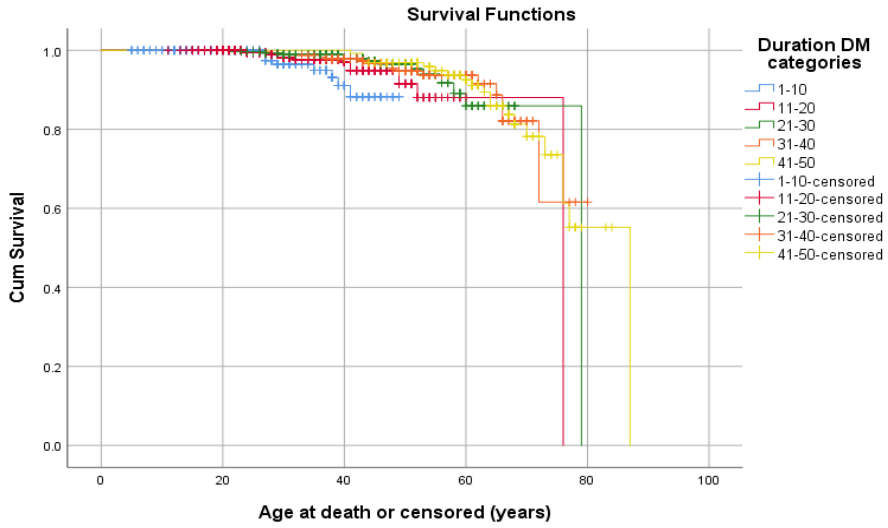


Figure 4.33: Survival curve according to the duration of diabetes (years) in people with T1D in the Wirral.

4.9.4. Year of diagnosis and survival time

Figure 4.34 shows the survival curve according to the year of diagnosis in people with T1D in the Wirral.

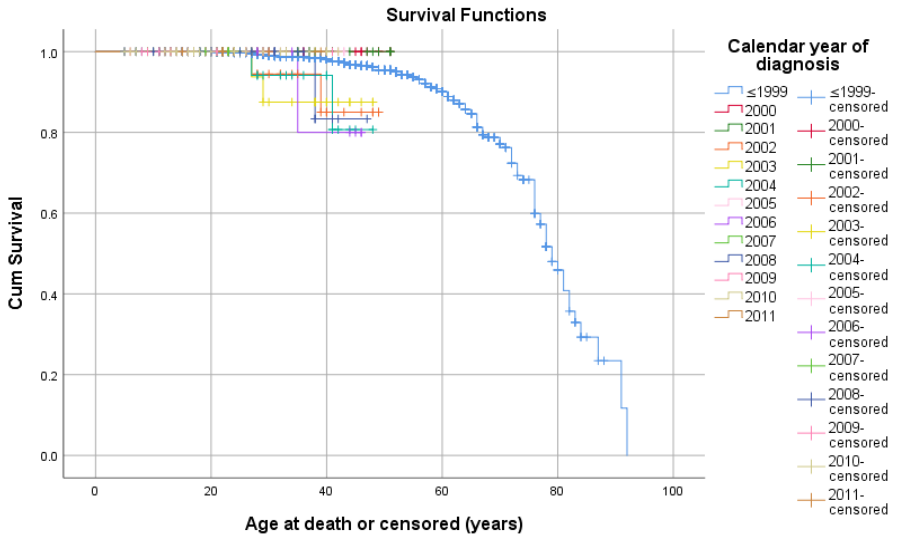


Figure 4.34: Survival curve according to the year of diagnosis in people with T1D

4.9.5. Index of multiple deprivations (IMD) and survival time

The optimum median survival period for males, was found in the third quintile (average) with median survival times of 78.940 years [95% CI: 74.958 – 82.922], and in quintile 2 (above average) for females and T1D population having a median survival of 80.179 years [95% CI: 74.081 – 86.277], and 79.409 years [95% CI: 74.452 – 84.367] respectively.

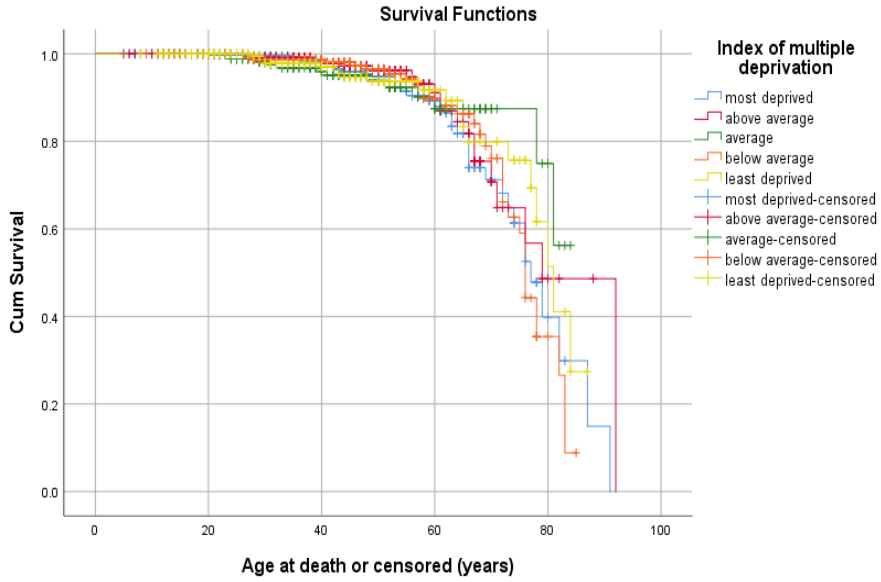


Figure 4.35: Survival curve according to the IMD (quintiles) in people with T1D

For the most deprived, males had longer median survival time 76.109 years [95% CI: 72.251 – 79.968] as compared to females 73.820 years [95% CI: 68.684 – 78.957]. The difference in median survival time for this group was 3 years. Figure 4.35 illustrates the survival curve according to the IMD (quintiles) in people with T1D.

4.9.6. HbA_{1c} and survival time

The relationship between the various subgroups and HbA_{1c} was not statistically significant (p-value=0.607). For those with levels of $HbA_{1c} \leq 5.9\%$ (41mmol/mol), the average age at death was 59.101 years [95% CI: 45.607 – 72.595]. As illustrated in Table 4.20 and Figure 4.36.

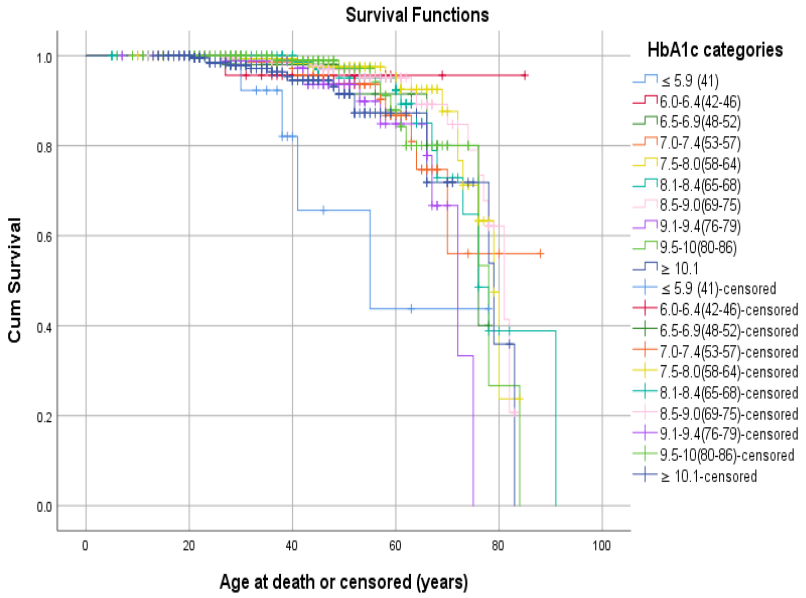


Figure 4.36: Survival curve according to serum HbA_{1c} (%) in people with T1D in the Wirral.

The overall trend follows a sinusoidal pattern with the optimum survival time noted with those having HbA_{1c} values of 6.0-6.4(42-46) mmol/mol with median survival of 82.478 years [95% CI: 77.644 – 87.312].

4.9.7. Smoking status and survival time

The survival curve according to smoking status is illustrated in Figure 4.37. Overall, those that never smoked survived longer than those who smoked had a median survival time of 78.518 years [95% CI: 75.634 – 81.401] and 73.104 years [95% CI: 69.584 – 76.625] respectively.

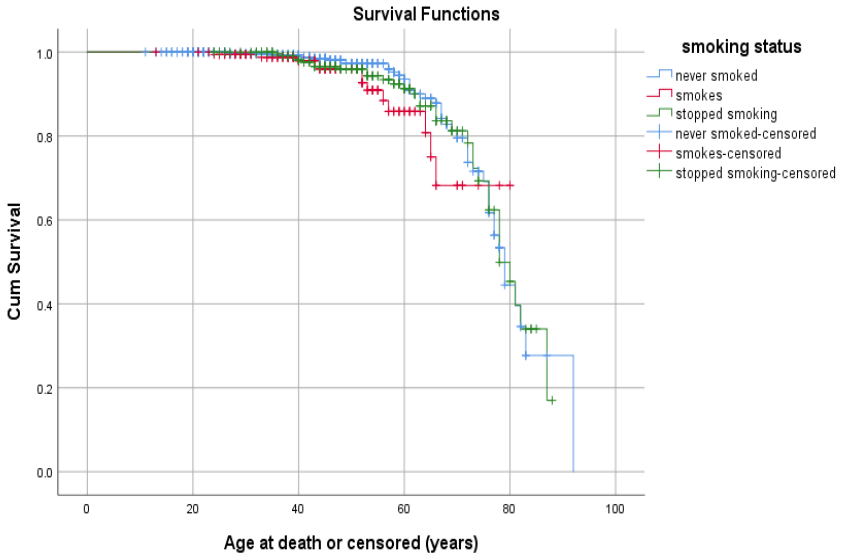


Figure 4.37: Survival curve according to the smoking status in people with T1D in the Wirral

However, the difference between smokers and no-smokers was more apparent in the female cohort where there was the 8-year difference in median survival times.

4.9.8. Body mass index (BMI) and survival time

Figure 4.38 illustrates the survival curve associated with the various categories of BMI. The median survival time for overall T1D population was 73.000 years [95% CI: 65.562 - 84.438]. BMI categories of 35.0 - 39.9 and ≥ 40 (kg/m^2) are noted to have reduced survival times of 40.000 years [95% CI; 22.396 - 57.604] in males, 61.000 years [95% CI: 48.998 - 73.002] in females, and 61.000 years [95% CI: 48.998 - 73.002] in the total T1D population.

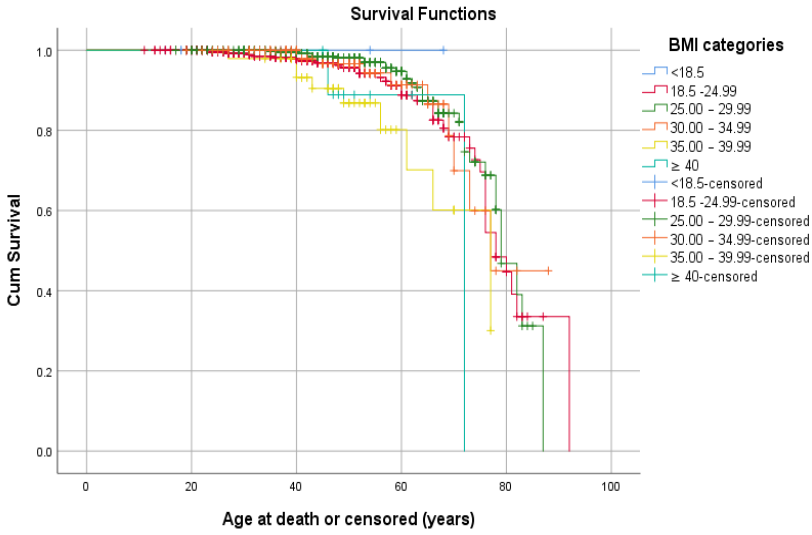


Figure 4.38: Survival curve according to the BMI (kg/m^2) in people with T1D in the Wirral

Those with normal BMI range had median survival times of 68.000 years [95% CI: 52.177 - 83.823] for males, 66.000 years [95% CI: 55.451 - 76.549] for females, and 67.000 years [95%

CI: 52.282 - 85.718]. Incidentally, those with BMI ≤ 18.4 kg/m^2 had higher survival times than those with normal BMI. This is probably due to the skewness of the population, as a large proportion of participants in this cohort were in their pre-teen and teenage years.

Serum creatinine and survival time

The median survival times found in those with normal serum creatinine levels, were median survival of 78.723 years [95% CI: 75.711 – 81.735] for males, 77.991 years [95% CI: 74.287 – 81.695] for females and 78.522 years [95% CI: 75.763 – 81.281] for T1D.

Figure 4.39: Survival curve according to serum creatinine levels (µmol/l) in people with T1D in the Wirral

A gradual decrease in median survival was noted as serum creatinine levels increased above the normal levels. The overall median survival for T1D according to serum creatinine levels was 76.995 years [95% CI: 75.060 – 78.930]. Overall, men and women had almost similar median survival times with statistically relevant relationship (p-value = <0.001). Figure 4.39 shows the survival curves for the various serum creatinine levels.

4.9.9. Systolic blood pressures and survival time

Median survival time for various systolic blood pressure ranges reveals a sinusoidal pattern. The overall average survival time for T1D population is 69 years [95%CI: 65.329 - 72.671].

Figure 4.40: Survival curve according to systolic blood pressure (mmHg) in people with T1D.

The lowest median survival period in this cohort was identified in those who had SBP range of 100-119, having a survival period of 57 years in males, females and the overall T1D population. The relationship of the various subgroups was not statistically significant (p-value=0.483). Figure 4.40 illustrates the survival curve for SBP.

4.9.10. Diastolic blood pressure and survival time

Table 4.20 shows the various categories of DBP and their median survival rates. The trend showed a reduction in survival time as the DBP increased. The lowest median survival was recorded in those who had DBP ≥100mmHg, having median survival times of 46.667 years 46.667 [95%CI: 38.132 - 38.132] for males, 65 years [95%CI: 60.842 - 69.158] for females and 62 years [95%CI: 24.207 - 99.793] for T1D.

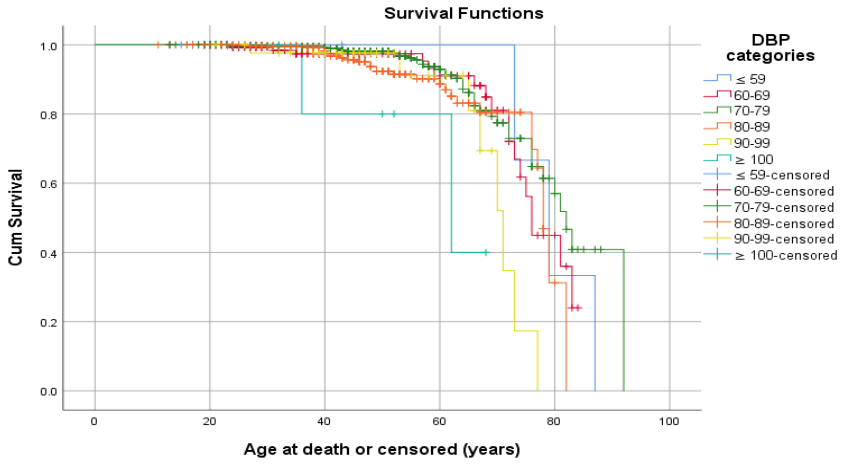


Figure 4.41: Survival curve according to the diastolic blood pressure (mmHg) in people with T1D, in the Wirral

There was a difference of 19 years in survival time between females and males in those with DBP ≥100mmHg. The overall the median survival for DBP was 77.806 years [95% CI: 75.493 – 79.452] in males, 76.225 years [95% CI: 73.245 – 79.206] in females and 79.000 years [95% CI: 76.284 – 81.716] for the overall T1D population. The relationships between the various groups were statistically significant (P-value= 0.008). Figure 4.41 illustrates the survival curve for DBP.

4.9.11. Total Cholesterol and survival time

The survival curve according to the various categories of cholesterol levels is illustrated by figure 4.42. Overall, males, females and T1D population had median survival times of 77.191 years [95% CI: 74.962 – 79.412], 76.062 years [95% CI: 72.941 – 79.184], and 76.000 [72.184 – 82.844].

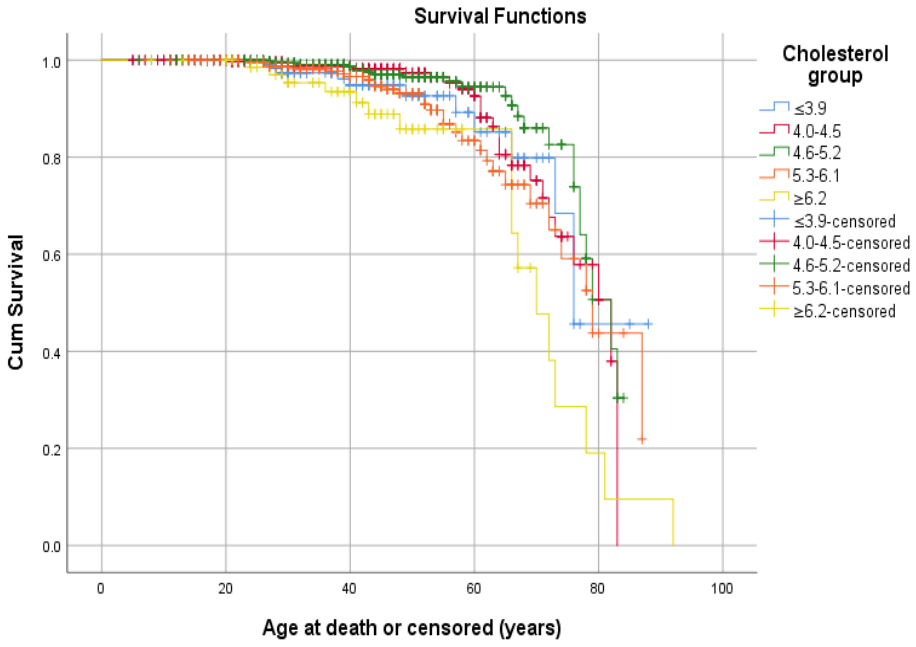


Figure 4.42: Survival curve according to the total Cholesterol (mmol/l) in people with T1D

For the overall population, higher levels of cholesterol resulted in reduced survival times. Those with levels of cholesterol of 5.3-6.1 and ≥6.2 mmol/l had median survival times of 70.000 years [95% CI: 63.128 – 76.872] and 66.000 years [95% CI: 60.895 – 82.105] respectively as compared to 76.000 years [95% CI: 71.184 – 81.844] in those with levels of ≤3.9mmol/l. The association between the various groups was statically relevant (p-value<0.002).

4.9.12. High-density lipoproteins [HDL] and survival time

Although there was little differentiation between the various subgroups, those who with HDL levels of 0.4-0.7 mmol/l had an average survival time of 71.000 years [95% CI: 62.000 - 86.000] as compared to 68.000 years [95% CI: 62.045 - 89.955] in those with HDL levels ≥ 1.6 mmol/l.

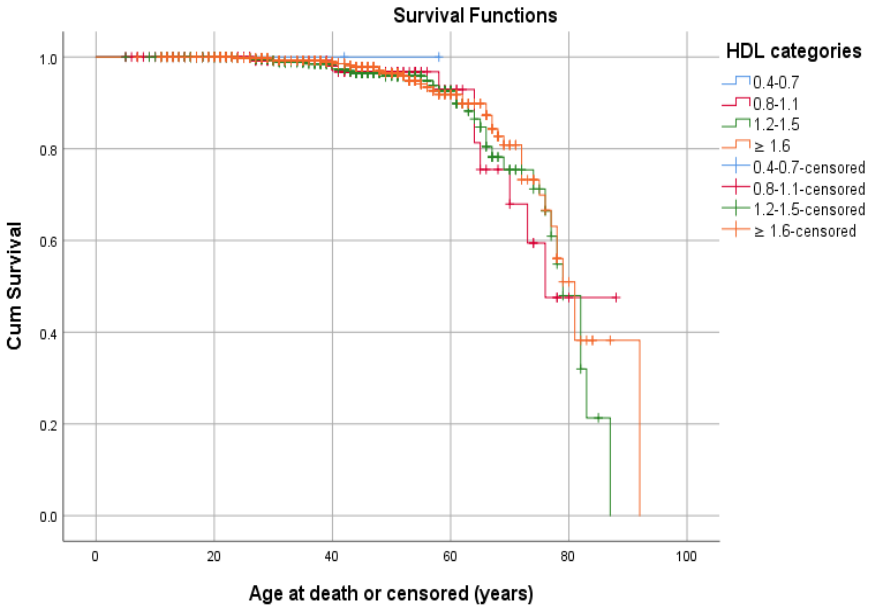


Figure 4.43: Survival curve according to HDL (mmol/l) in people with T1D in the Wirral

The was a gradual decrease in median survival with increase in HDL levels. In the subgroup that had HDL levels of 0.4-0.7 mmol/l, females had higher median survival than males with a difference of 4 years, while for those having HDL levels ≥ 1.6 mmol/l males had higher median survival than females with a difference of 2 years. The survival curve showing the interaction of the various subgroups is illustrated in Figure 4.43.

4.9.13. Triglycerides [TG] (mmol/l) and survival time

Values of TG levels of ≤ 1.6 mmol/l had the best median survival times, having median survival of 81.000 years [95% CI: 78.152 – 83.848] for males, 78.000 years [95% CI: 71.840 – 84.160] for females and 81.000 years [95% CI: 77.007 – 84.993] in T1D population. For TG levels ≥ 2.3mmol/l, median survival times for males, females and T1D were 70.000 years [95% CI: 60.933 – 79.067], 72.000 years [95% CI: 62.015 – 81.985], and 70.000 years [95% CI: 64.220 – 75.780] respectively.

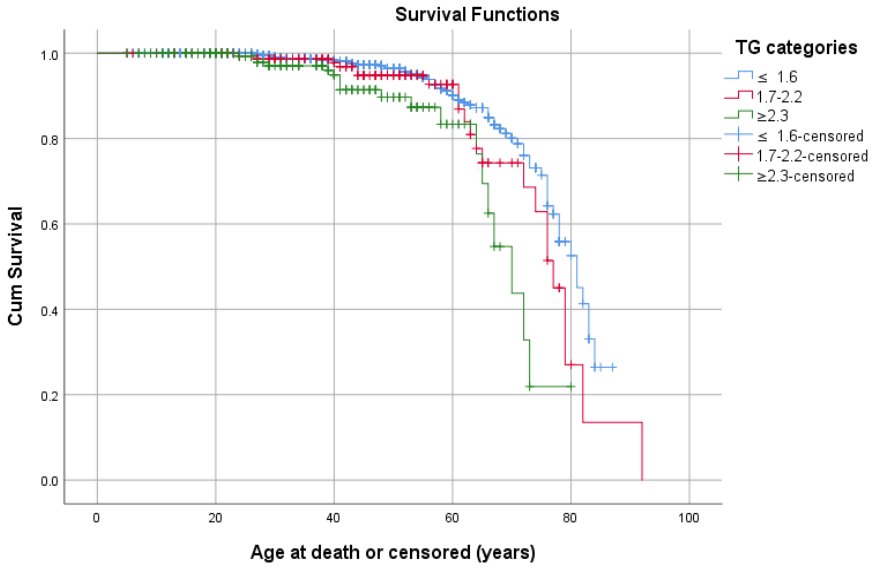


Figure 4.44: Survival curve according to serum Triglyceride level (mmol/l) in people with T1D, in the Wirral

This represented a minimum difference of 3 years between those with values ≤ 1.6 mmol/l and those with values ≥ 2.3mmol/l. The overall median survival for this cohort was 79.000 years [95% CI: 76.061 – 81.939]. The association between the various subgroups was statistically significant (p-value <0.001). The survival curve showing the associations of the various groups is illustrated in figure 4.44.

4.9.14. Low-density lipoprotein [LDL] (mmol/l) and survival time

In males, there was a definite trend to indicate reduced survival as levels of LDL increased; this trend was also replicated in females and total T1D population except in those with levels of ≥ 5.0 mmol/l.

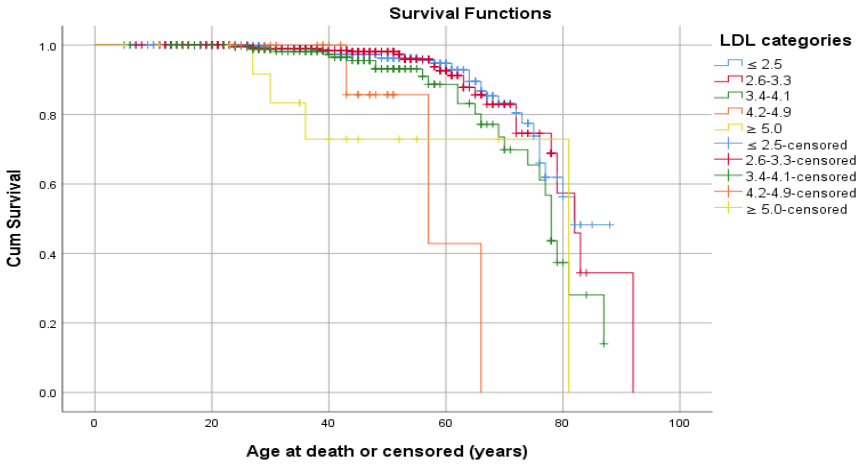


Figure 4.45: Survival curve according to the serum LDL (mmol/l) in people with T1D, in the Wirral

The differences between those having LDL levels of ≤ 2.5 mmol/l and 4.2 - 4.9 mmol/l was 31 years in males, 16 years in females and 21 years in T1D population. The median survival for this cohort was 78.611 years [95% CI: 76.424 – 80.797]. The relationship between the various subgroups was statistically significant (p-value <0.001). This relationship is illustrated by the survival curve Figure 4.45.

4.9.15. Total Cholesterol: HDL ratio and survival times

Reduce median survival times were observed with increasing values for TC: HDL ratios. Those who had ratios of ≤ 3.5 had median survival times of 82.000 years [95% CI: 79.317 – 84.683] in males, 78.000 years [95% CI: 73.539 – 82.461] in females and 81.000 years [95% CI: 77.205 – 84.795] in T1D.

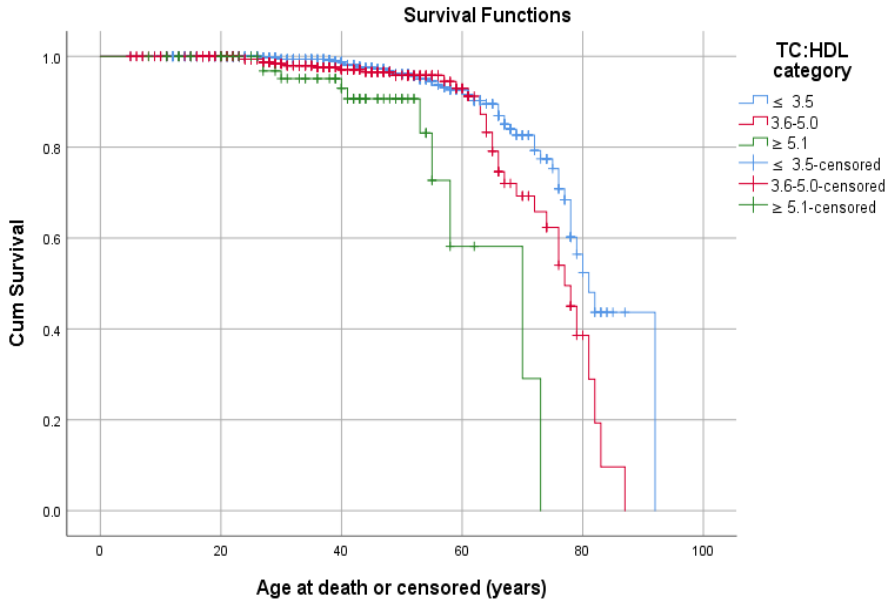


Figure 4.46: Survival curve according to the total Cholesterol-to-HDL ratio in people with T1D

In contrast, those with ratios ≥ 5.1 had median survival times of 58.000 years [95% CI: 49.826 – 66.174] for males, 73.000 years [95% CI: 61.078 – 75.783] for females, and 70.000 years [95% CI: 52.128 – 87.872] for T1D. This indicates a difference between the 2 subgroups of ratios was 24 years in males, 5 years in females, and 11 years in T1D. There was minimal difference between males and females and the relationship between the various subgroups was statistically significant (p-value < 0.001). This is shown by the survival curve Figure 4.46.

4.9.16. Low-Density Lipoprotein LDL: HDL ratio and survival times

A similar trend of reducing median survival times with increasing ratios was observed with LDL: HDL ratios. Figure 4.47 indicates the curve of T1D population according to their LDL:

HDL ratios. This trend indicates an inverse relationship; as higher values were associated with poorer survival in the various subgroups.

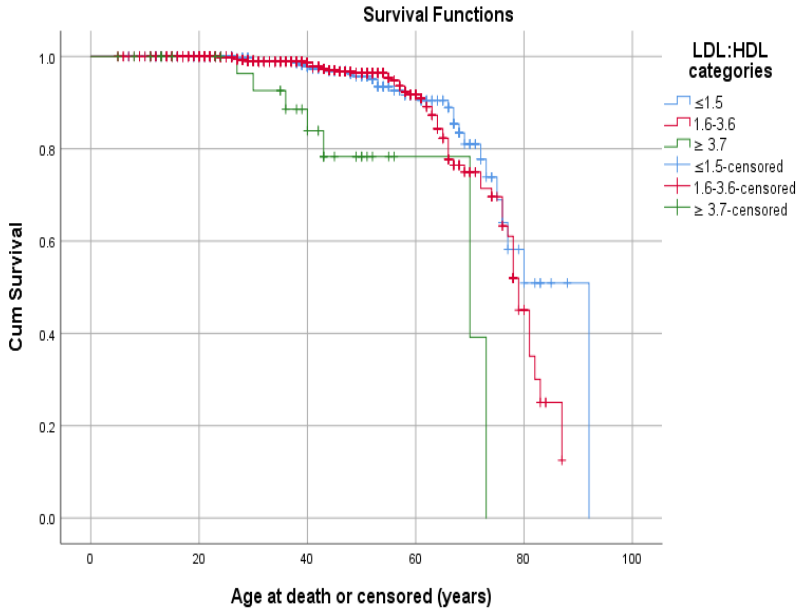


Figure 4.47: Survival curve according to the LDL: HDL ratio in people with T1D in the Wirral

The difference between the various subgroups was statistically significant (p-value <0.001). The difference between those with ratios ≤ 1.5 and ≥ 3.7 was 21 years for males, 4 years for females and 17 years for T1D. Males had higher median survival than females of a minimum difference of 3 years for those with ratios 1.6-3.6 and a maximum difference of 13 years in those with ratios of ≥ 3.7.

4.10 Hazard Ratios

The hazard ratio (HR) is defined as a measure of the likelihood of mortality at a specified time value of the predictors or risk. Following modelling, one potential benefit is to ascertain which of the predictors or combination of predictors influence the median survival. This also creates a platform to ascertain prognosis of the disease condition. Figure 4.48 illustrates the survival curve for people with T1D with gender differentiation.

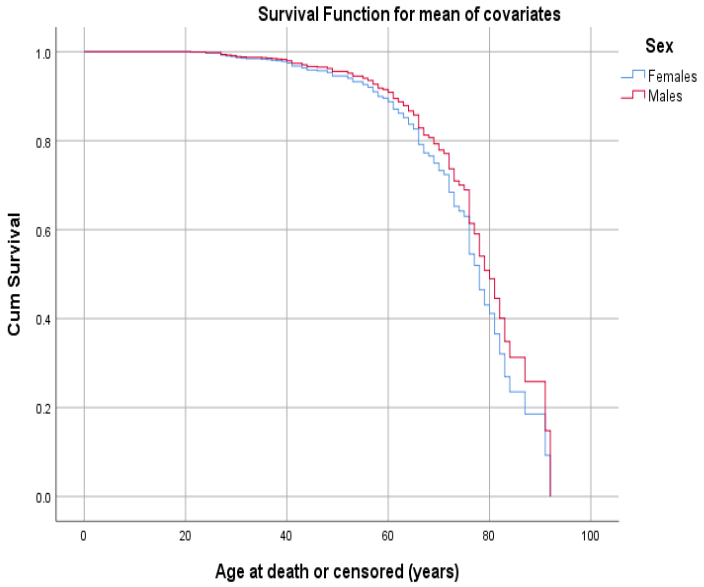


Figure 4. 48: Survival curve for people with T1D, in the Wirral between years 2000 and 2012, according to gender.

Females had better survival than men during the period under consideration (-2 log likelihood statistics = 2202.60; X^2=.004; p-value 0.949). The multivariate analysis of the predicting variables and their corresponding HR, 95%CI and p-values as illustrated in Table 4.23. Gender, BMI (kg/m2), index of multiple deprivations, High-density lipoproteins HDL (mmol/l), TC/HDL ratio, LDL/HDL ratio, Age at diagnosis, Duration of diagnosis were not effective in the ascertaining the probability of mortality in T1D.

Table 4.21: Predicting factors and hazard ratios with their corresponding 95% CI

Predicting factors	Hazard ratios [95 % CI]	p-values
Gender	0.962 [0.231 – 2.070]	0.692
Systolic BP (mmHg)	1.666 [0.669- 4.149]	0.273
Diastolic BP (mmHg)	1.105 [0.414- 2.953]	0.842
Smoking status	1.241 [0.606- 2.540]	0.556
Serum creatinine (µmol/l)	1.964 [1.088- 3.545]	0.025
HbA_{1c} (%)	1.101 [0.812- 1.493]	0.534
BMI (kg/m^2)	0.923 [0.486 - 1.752]	0.806
IMD quintiles	0.722 [0.474- 1.100]	0.129
Total Cholesterol (mmol/l)	1.829 [0.712 - 4.700]	0.210
High-density lipoproteins (mmol/l)	0.319 [0.066- 1.543]	0.156
Low-density lipoproteins (mmol/l)	1.346 [0.426- 4.254]	0.613
Triglycerides (mmol/l)	1.286 [0.545- 3.036]	0.566
TC/HDL ratio	0.496 [0.094- 2.622]	0.409
LDL/HDL ratio	0.595 [0.123- 2.888]	0.520
Age at diagnosis	0.799 [0.868 - 0.939]	0.326
Duration of diagnosis	0.964 [0.510- 1.250]	0.559

In contrast, the following predicting factors were linked with greater risk of mortality in T1D; SBP (mmHg), DBP (mmHg), smoking status, serum creatinine (µmol/l), HbA_{1c} (%), Total Cholesterol (mmol/l), Low-density lipoproteins LDL (mmol/l), and Triglycerides TG (mmol/l). However, all the predicting variables considered were statistically insignificant but clinically significant (p-value >0.05).

Computation was done to adjust for predictors that did not cross the 1.0 value line to determine the significant variable on which the Cox model was based; there was no alteration to those shown in table 4.24. Values of the coefficients for the predictor variables of gender, BMI (kg/m2), IMD quintiles, HDL (mmol/l), TC/HDL ratio, LDL/HDL ratio, Age at diagnosis, and duration of diabetes (years) were computed to evaluate if the Cox model was dependent any of them. Table 4.22 shows the results elaborating on their HR and 95% CI.

Table 4.22: Explanatory factors which the Cox model did not depend on after adjustments.

Predicting factors	**Hazard ratios [95 % CI]**	**p-values**
Gender	0.784 [0.356 - 1.727]	0.546
BMI (kg/m2)	1.135 [0.779 - 1.653]	0.509
IMD quintiles	0.872 [0.450 - 2.186]	0.283
High-density lipoproteins (mmol/l)	0.992 [0.450 - 2.186]	0.983
TC/HDL ratio	1.615 [0.643 - 4.053]	0.308
LDL/HDL ratio	1.465 [0.598 - 3.591]	0.403
Age at diagnosis	0.816 [0.623 - 1.068]	0.139
Duration of diagnosis	0.782 [0.462 - 1.324]	0.361

Following adjustments, BMI (kg/m2), TC/HDL ratio and LDL/HDL ratio were found to be clinically significant but statistically insignificant, having HR of 1.135 [95% CI: 0.779 - 1.653], 1.615 [95% CI: 0.643 - 4.053], and 1.465 [95% CI: 0.598 - 3.591] respectively.

Using bivariate analysis for correlation between the predicting factors, the analysis showed the strongest correlation was between gender and BMI (kg/m2) with Pearson correlation of 0.219, p-value 0.001. The following predicting factors had poor and positive correlations with gender; smoking status, SBP (mmHg), Total Cholesterol (mmol/l), Low-density lipoproteins LDL (mmol/l), and TSH levels. Negative and poor correlations were observed in predicting variables of age group at diagnosis, Creatinine levels, HbA_{1c} (%), DBP (mmHg), TG, TC: HDL, LDL: HDL, Duration of diabetes, and index of multiple deprivations.

The categorisation of the predicting variables and a further application of the Cox regression model yielded results as displayed in Table 4.25. The predictive risk of mortality for females was slightly lower than males' but not statistically significant.

Table 4.23: Cox proportional hazard model of predicting factors and hazard ratio, with their corresponding 95% CI and p-values in T1D

Predicting factor	**Hazard ratio [95%CI]**	**p-value**
Females	0.930 [0.164- 5.287]	0.935
Males	1.000 [reference]	
Age of diagnosis (years)		
0 – 4	1.000 [reference]	-
5 – 9	0.666 [0.00007- 29.200]	0.945
10 – 14	1.919 [0.027- 13.788]	0.764
15 – 19	1.153 [0.042- 31.457]	0.933
20 – 24	1.419 [0.042- 48.490]	0.846
25 – 29	1.508 [0.086- 26.401]	0.779
30 – 34	0.864 [0.055- 13.598]	0.917
35 – 39	1.012 [0.094- 10.949]	0.992
Index of Multiple Deprivation		
Quintile 1(most deprived)	1.000 [reference]]	-
Quintile 2(above average)	2.123 [0.162- 27.768]	0.566
Quintile 3(average)	1.350 [0.063- 29.046]	0.848
Quintile 4(below average)	1.304 [0.056- 30.183]	0.868
Quintile 5(least deprived)	1.888 [0.117- 30.544]	0.654
Smoking status		
Never smoked	1.000 [reference]	0.898
Current smoker	1.065 [0.132- 8.602]	0.953
Ex-smoker	1.556 [0.205- 11.800]	0.669
BMI (kg/m^2)		
≤ 18.4	1.000 [reference]	0.999
18.5 - 24.9	0.548 [0..00008 - 36.76]	0.915
25.0 - 29.9	1.045 [0.010- 108.709]	0.985
30.0 - 34.9	0.883 [0.008- 93.630]	0.958
35.0 - 39.9	1.479 [0.013- 162.753]	0.870
≥ 40	1.352 [0.004- 437.779]	0.919
HbA_{1c} (%)		
≤ 5.9 (41)	1.000 [reference]	-
6.0-6.4(42-46)	0.665 [0.0001- 30.911]	0.941
6.5-6.9(48-52)	0 .803 [0.004- 156.436]	0.935
7.0-7.4(53-57)	1.095 [0.031- 38.889]	0.960
7.5-8.0(58-64)	0.739 [0.043- 12.789]	0.835
8.1-8.4(65-68)	0.882 [0.029- 27.227]	0.943
8.5-9.0(69-75)	0.652 [0.039- 10.975]	0.766
9.1-9.4(76-79)	0.719 [0.018- 28.867]	0.861
9.5-10(80-86)	0.586 [0.305 – 12.126]	0.998

≥ 10.1	0.599 [0.027- 13.493]	0.747
Serum creatinine (µmol/l)		
≤ 61	1.000 [reference]	0.057
62-106	0.250 [0.066- 40.594]	0.322
107-129	0.072 [0.005- 1.080]	0.057
130-149	0.082 [0.003- 1.926]	0.120
≥ 150	0.047 [0.00043- 53.035]	0.395
Low density lipoprotein [LDL] (mmol/l)		
≤ 2.5	1.000 [reference]	0.985
2.6 - 3.3	4.037 [0.0002- 62505.661]	0.777
3.4 - 4.1	5.441 [0.0004- 59515.447]	0.721
4.2 - 4.9	6.390 [0.002- 25278.350]	0.661
≥ 5.0	1.430 [0.0004- 4266.892]	0.930
High density lipoproteins [HDL] (mmol/l)		
0.4-0.7	1.000 [reference]	0.484
0.8-1.1	1.149 [0.024- 141.13]	0.963
1.2-1.5	1.156 [0.788 - 1.694]	0.343
≥ 1.6	1.160 [0.764 - 1.784]	0.473
Triglycerides [TG] (mmol/l)		
≤ 1.6	1.000 [reference]	0.484
1.7-2.2	0.959 [0 .053 - 17.295]	0.977
≥ 2.3	2.826 [0.144- 55.376]	0.494
Total Cholesterol (mmol/l)		
≤3.9	1.000 [reference]	0.987
4.0-4.5	0.252 [0.001- 62.932]	0.625
4.6-5.2	0.360 [0.002- 53.117]	0.688
5.3-6.1	0.333 [0.004- 27.619]	0.625
≥6.2	0.347 [0.007- 16.864]	0.593
Total Cholesterol: HDL ratio		
≤ 3.5	1.000 [reference]	0.916
3.6-5.0	0.554 [0.006- 52.541]	0.799
≥ 5.1	0.421 [0.005- 37.904]	0.706
Low-Density Lipoproteins: HDL ratio		
≤ 1.5	1.000 [reference]	0.917
1.6-3.6	0.294 [0.0001- 518.112]	0. 748
≥ 3.7	0.254 [0.0002-280.442]	0.702
Duration of Diabetes		
1-10	1.000 [reference]	0.688
11-20	0.177 [0.0003- 101.740]	0.827
21-30	5.816 [0.220- 153.507]	0.292
31-40	1.422 [0.080- 25.174]	0.810
41-50	0.744 [0.085- 6.501]	0.789

The HRs according to age group at diagnosis reflects a sinusoidal pattern with the highest HR recorded for the age group 10-14 years.

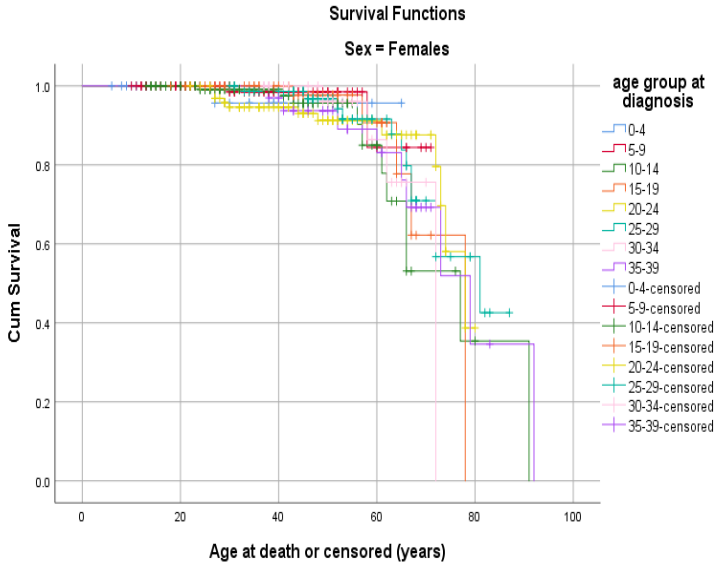


Figure 4.49: Survival curve for females with T1D according to their age at diagnosis (years)

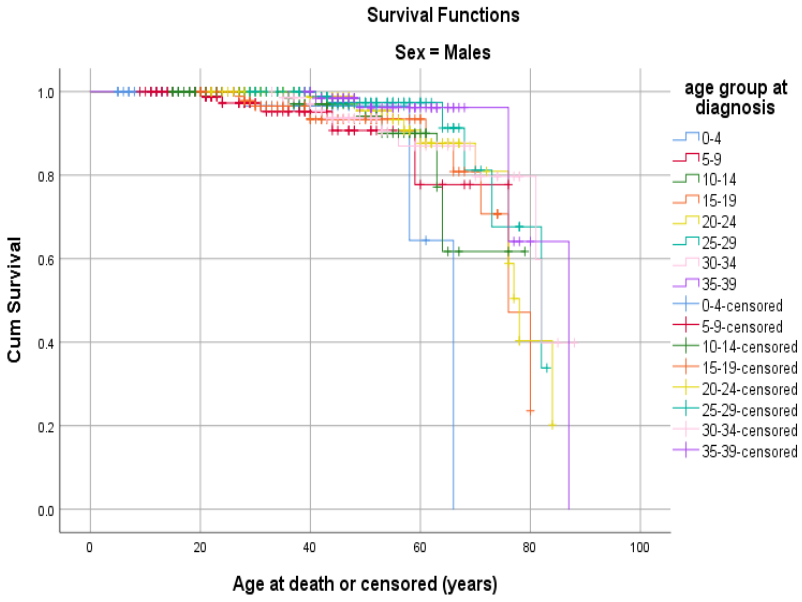


Figure 4.50: Survival curve for males with T1D according to their age at diagnosis (years)

Values for all the subgroups were not statistically significant. Excluding the age groups 5-9, 30-34, other age groups of 10-14, 15-19, 20-24, 25-29, and 35-39 had higher HRs as compared to the reference group of 0-4 years. Figures 4.49 and 4.50 illustrate the survival curves for females and males respectively according to their age at diagnosis with minimal differentiation. The index of multiple deprivations had extrapolated HRs for the various subgroups that were not statistically significant. Using the most deprived group as the reference group, the least

deprived quintile had a slightly increased predictive risk of mortality with HR 1.888 ([95% CI: 0.117- 30.544). Figures 4.51 and 4.52 show the survival curves for females and males respectively according to IMD.

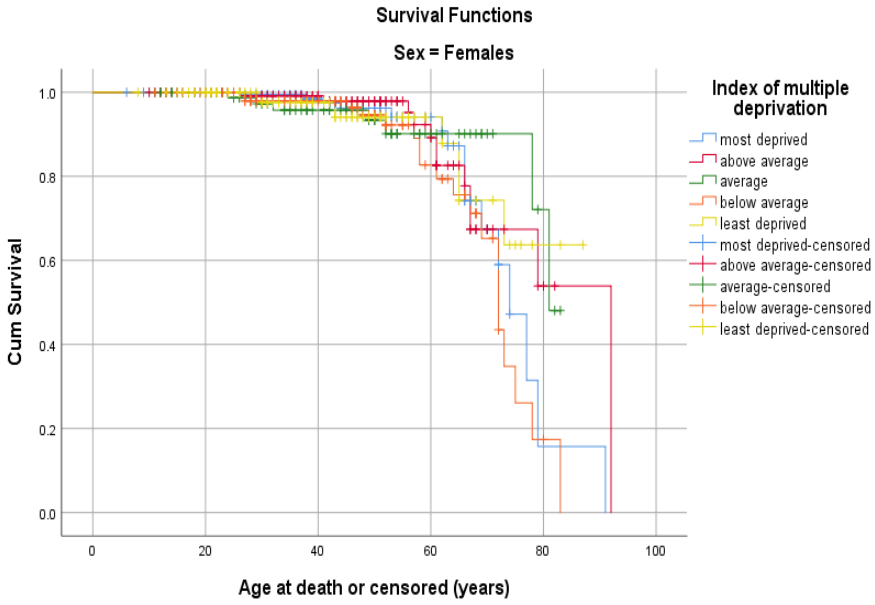


Figure 4.51: Survival curve for females with T1D in the Wirral according to their IMD quintile

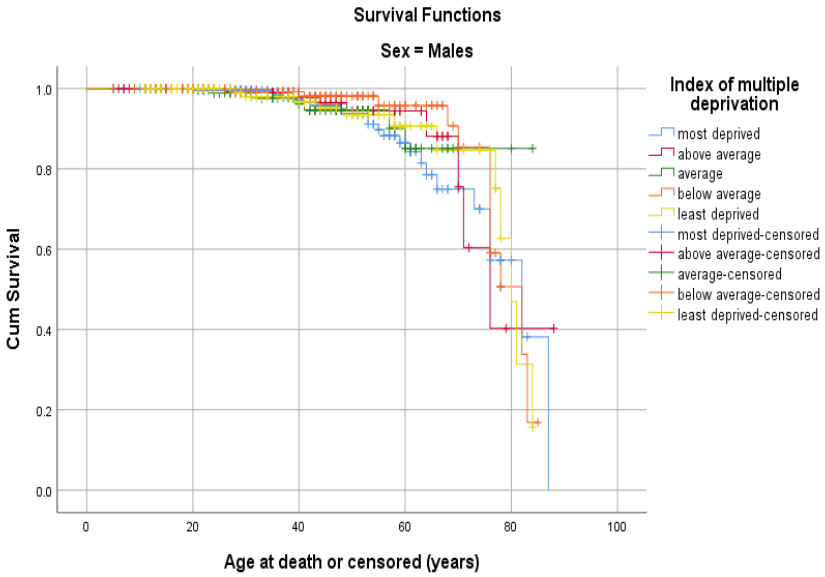


Figure 4.52: Survival curve for males with T1D in the Wirral according to their IMD quintile

According to smoking status, current smokers had a higher predictive risk of mortality as compared to non-smokers. Using non-smokers as the reference group, the HRs for current smokers and Ex-smokers were 1.065 [95%CI: 0.132 – 8.602], and 1.556 [95%CI: 0.205 – 11.800] respectively.

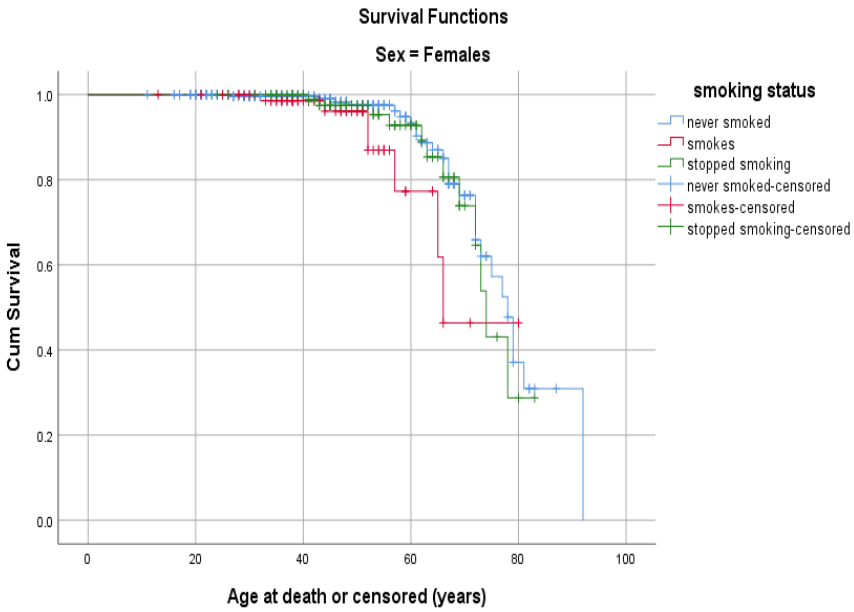


Figure 4.53: Survival curve for females with T1D, in the Wirral according to their smoking status

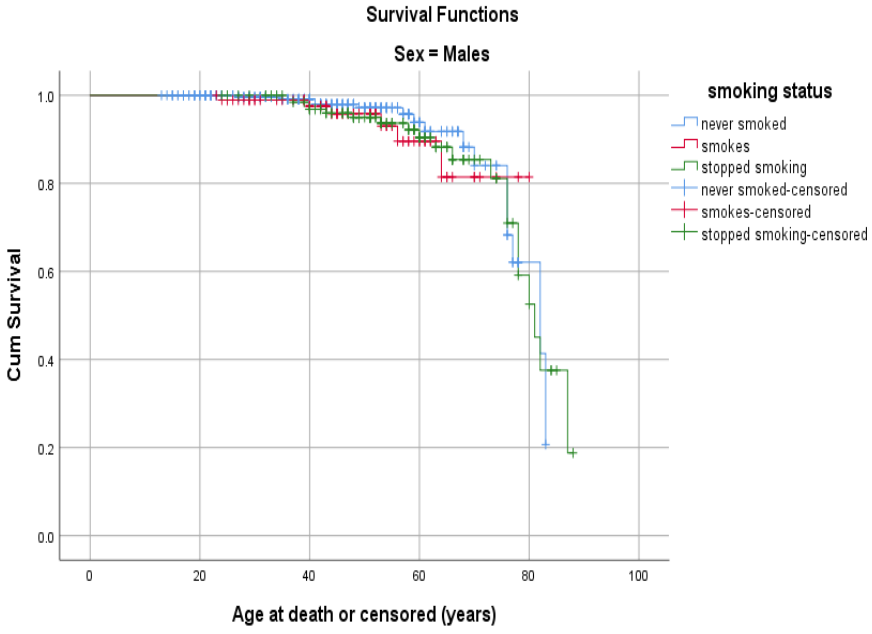


Figure 4.54: Survival curve for males with T1D, in the Wirral according to their smoking status

The HRs for those who never smoked and current smokers were not statistically significant. Figures 4.53 and 4.54 show the survival curves for females and males according to their smoking status. For BMI (kg/m^2), using the group with BMI $\leq$ 18.4 kg/m^2 as the reference group, the group having the lowest risk of death were those with BMI 18.5 - 24.9 having HR of 0.0548 [95%CI: 0.00008 – 36.76. The highest risk of death was in those BMI 35.0 - 39.9

(kg/m^2). Figures 4.55 and 4.56 illustrate the survival curves with gender differentiation according to BMI category.

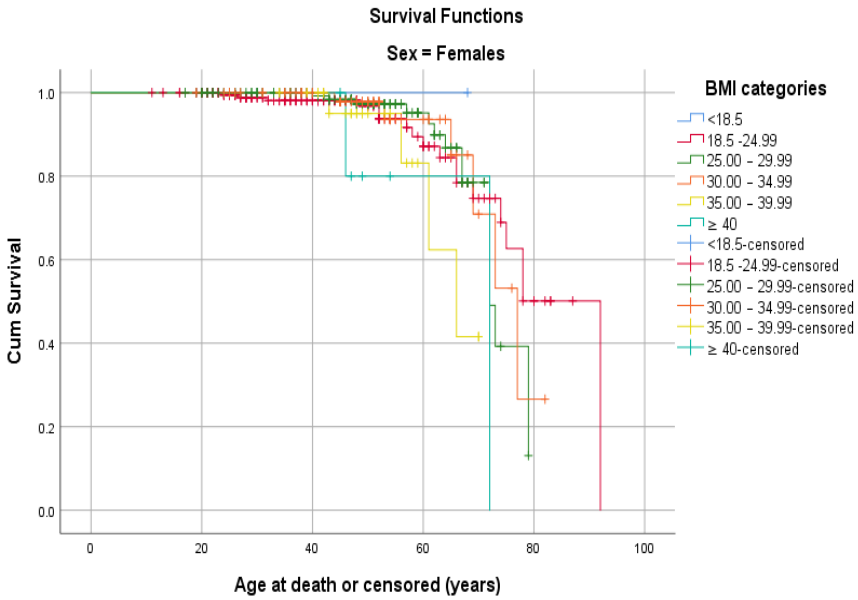


Figure 4.55: Survival curve for females with T1D in the Wirral, according to their BMI (kg/m^2)

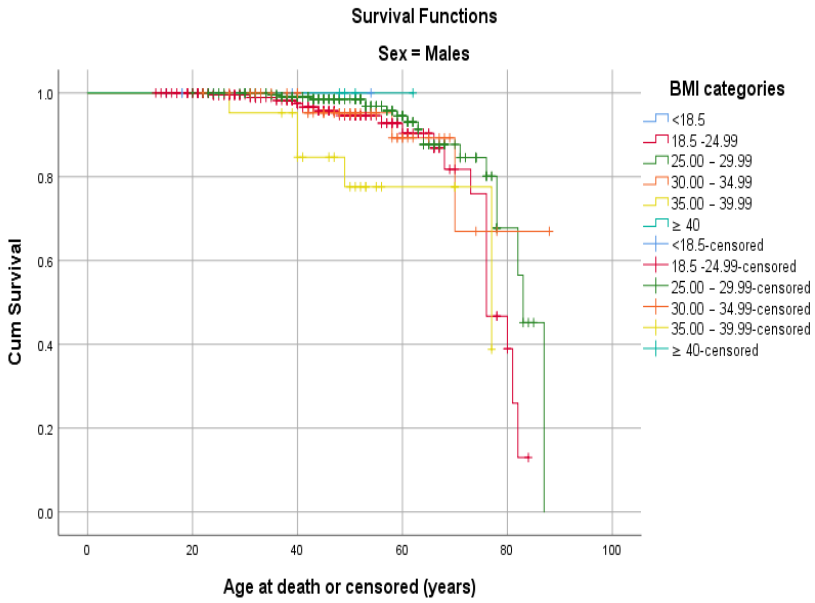


Figure 4.56: Survival curve for males with T1D in the Wirral, according to their BMI (kg/m^2)

There was no indication that HbA_{1c} (%) was a factor in ascertaining the probability of the occurrence of death. The overall trend followed a sinusoidal pattern Figures 4.57 and 4.58 show the survival curves for females and males according to their HbA_{1c} (%) levels.

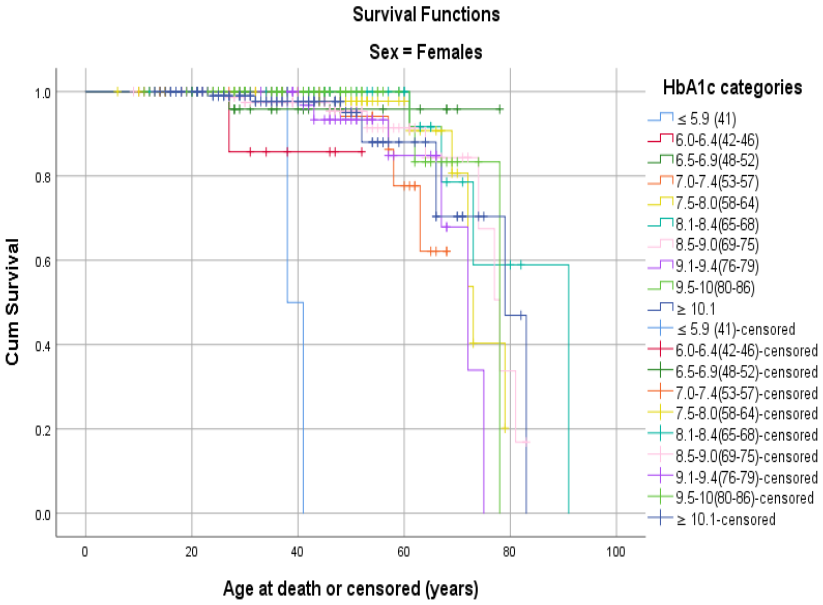


Figure 4.57: Survival curve for females with T1D in the Wirral according to their HbA_{1c} (%)

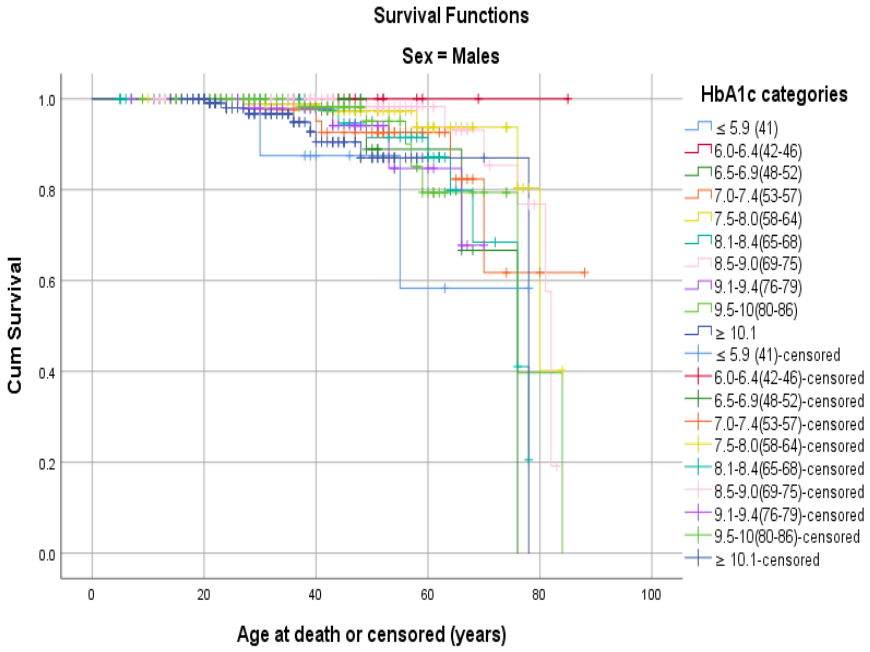


Figure 4.58: Survival curve for males with T1D in the Wirral according to their HbA_{1c} (%)

Values for HRs were not statistically significant. Values for serum creatinine were not effective in predicting the probability that mortality had occurred. Those with levels of 107-129 and 130-149 (µmol/l) had HRs of 0.072 [95%CI: 0.005 – 1.080], and 0.082 [95%CI: 0.003 - 1.926] respectively. Figures 4.59 and 4.60 reflect survival curves for females and males according to their serum creatinine levels.

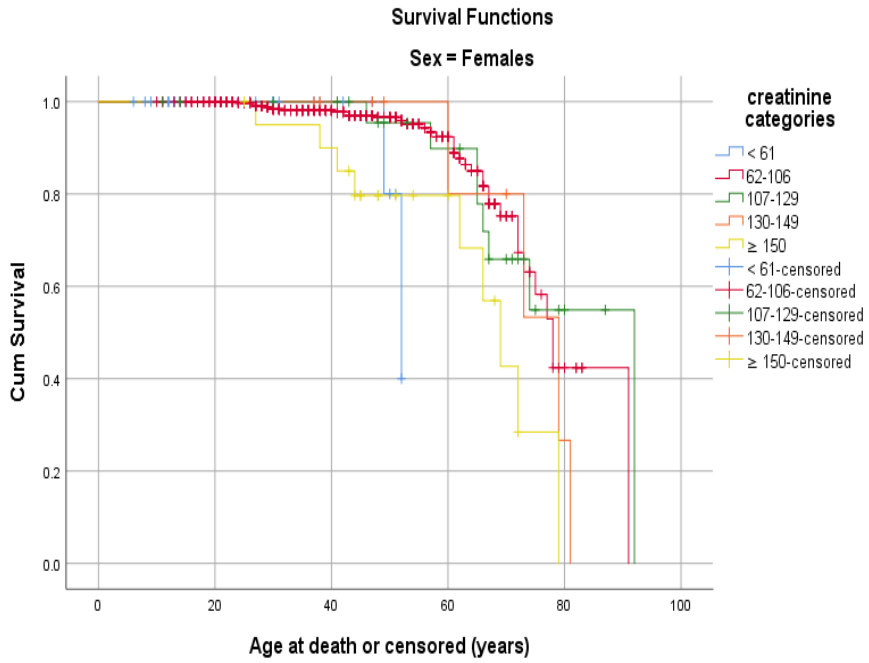


Figure 4.59: Survival curve for females with T1D in the Wirral, according to their serum creatinine levels (µmol/l)

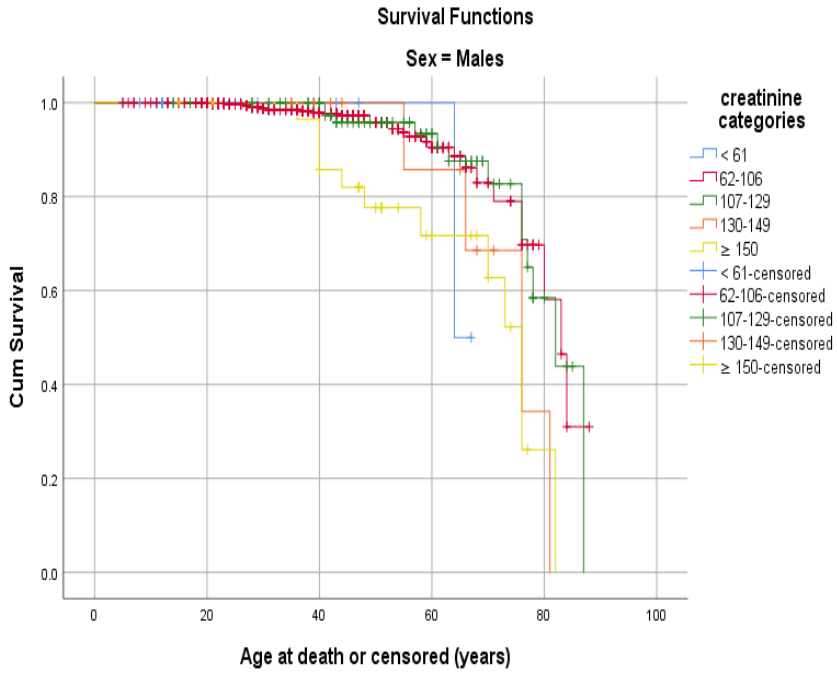


Figure 4.60: Survival curve for males with T1D in the Wirral, according to their serum creatinine levels (µmol/l)

There was an increase in mortality risk as LDL levels increased, this is shown by those having LDL levels in the subcategories 2.6 - 3.3, 3.4 - 4.1, and 4.2 - 4.9 (mmol/l) having HRs of 4.037 [95%CI: 0.0002 – 62505.6], 5.441 [95%CI: 0.0004 – 59515.45], and 6.390 [95%CI: 0.002 –

25278.35] respectively. Figures 4.61 and 4.62 show the survival curves for females and males according to their LDL levels.

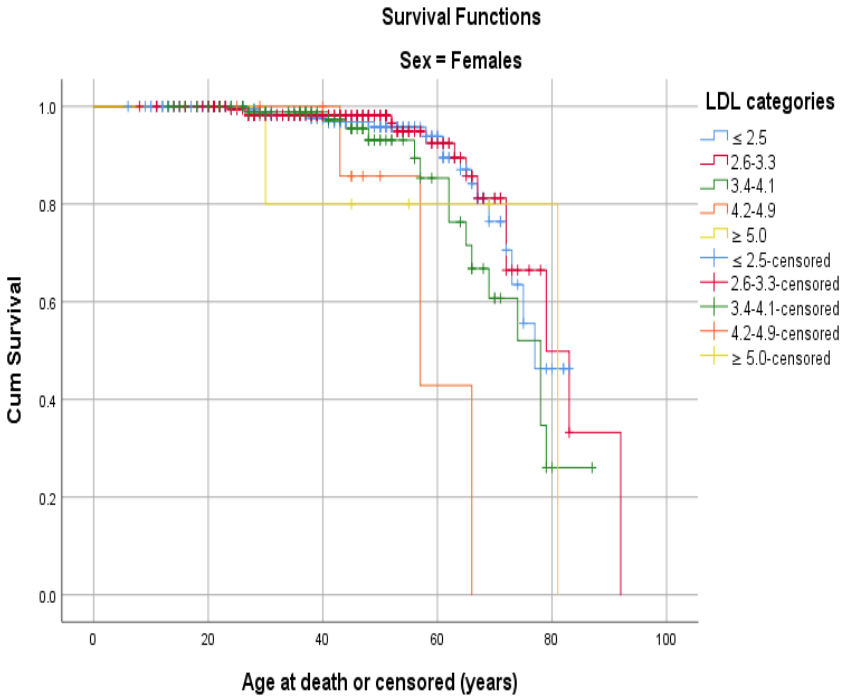


Figure 4.61: Survival curve for females with T1D in the Wirral, according to their serum LDL level (mmol/l)

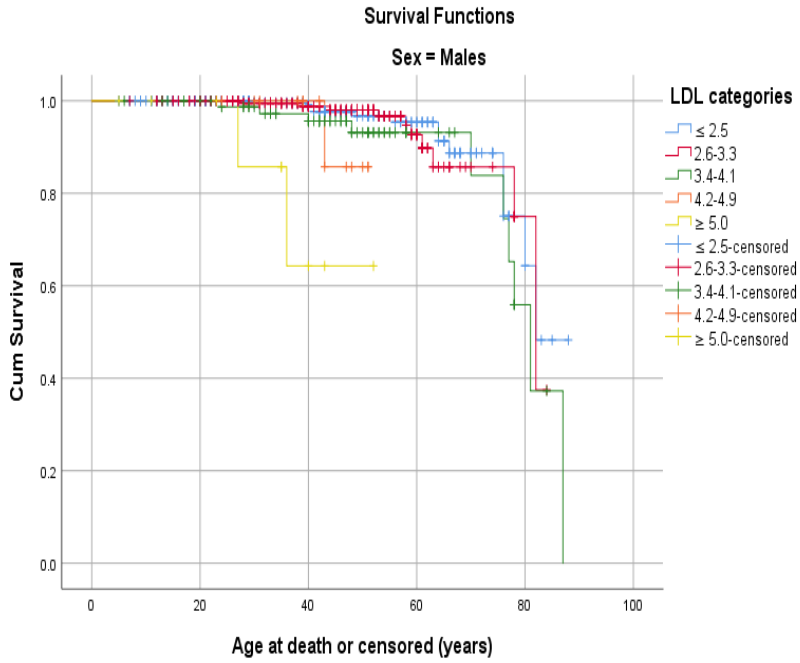


Figure 4.62: Survival curve for males with T1D in the Wirral, according to their serum LDL level (mmol/l)

Values for levels of HDL indicate that HDL was a predictive risk factor for the probability of mortality but not statistically significant. HDL levels 0.8-1.1, and 1.2-1.5, and ≥ 1.6 (mmol/l)

had HRs of 1.149 [95%CI: 0.024 – 141.13], 1.156 [95%CI: 0.788 - 1.94], and 1.160 [95%CI: 0.764 - 1.784] respectively. Figures 4.63 and 4.64 show the survival curves for females and males according to their HDL levels.

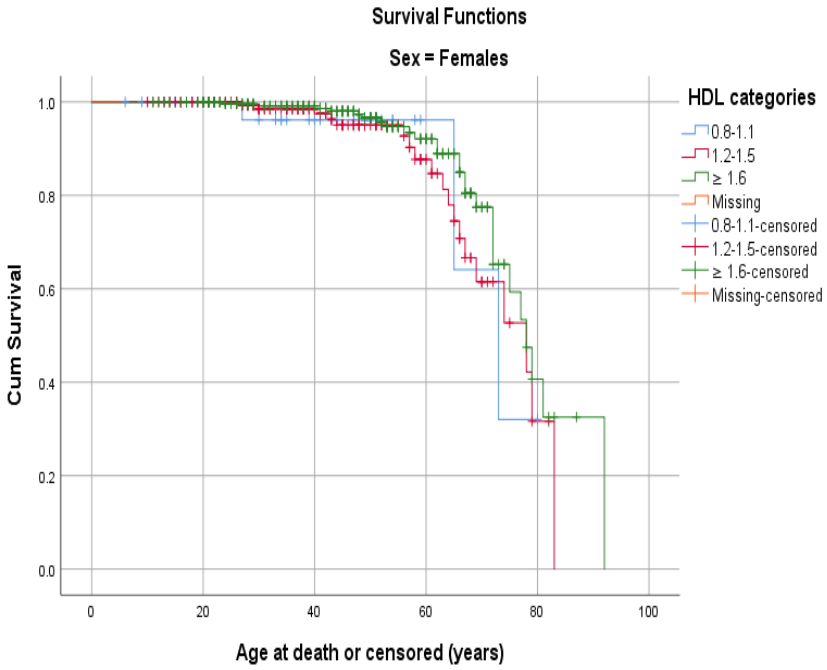


Figure 4.63: Survival curve for females with T1D in the Wirral, according to their serum HDL level (mmol/l)

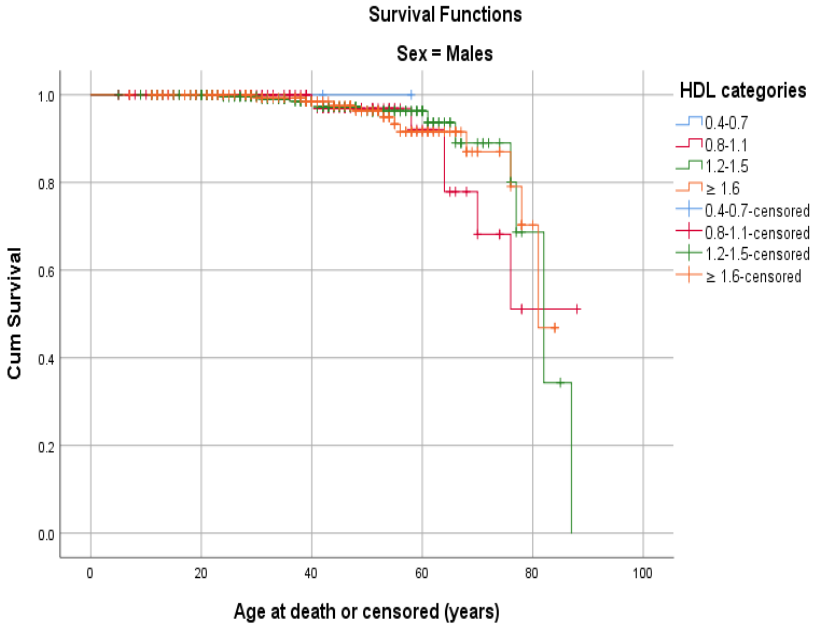


Figure 4.64: Survival curve for males with T1D in the Wirral, according to their serum HDL level (mmol/l)

Triglycerides [TG] (mmol/l) was not effective in predicting if the probability of mortality occurring. Values of between 1.7-2.2mmol/l had HR of 0.959 [95%CI: 0.538 – 17.295] but nor

statistically significant. Figures 4.65 and 4.66 show the survival curves for females and males according to their TG levels.

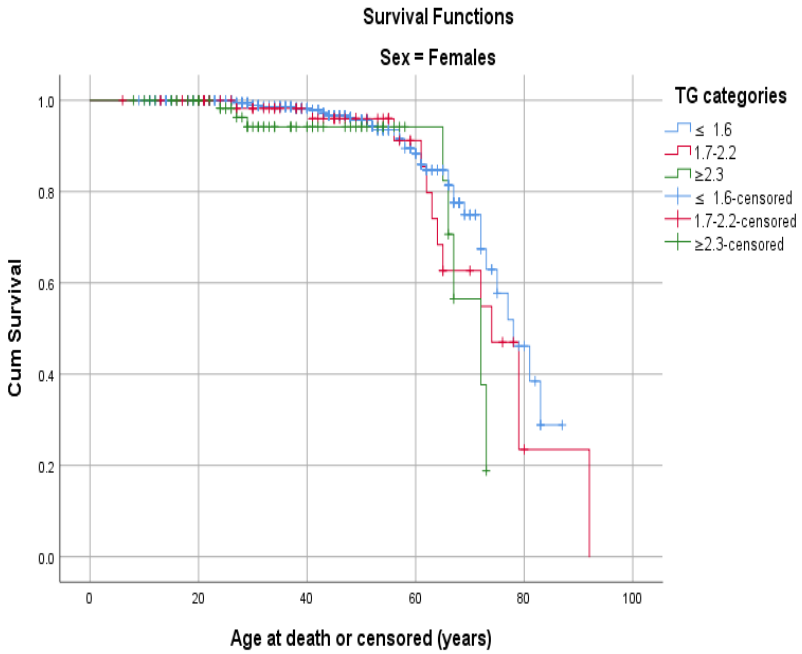


Figure 4.65: Survival curve for males with T1D in the Wirral, according to their serum TG levels (mmol/l)

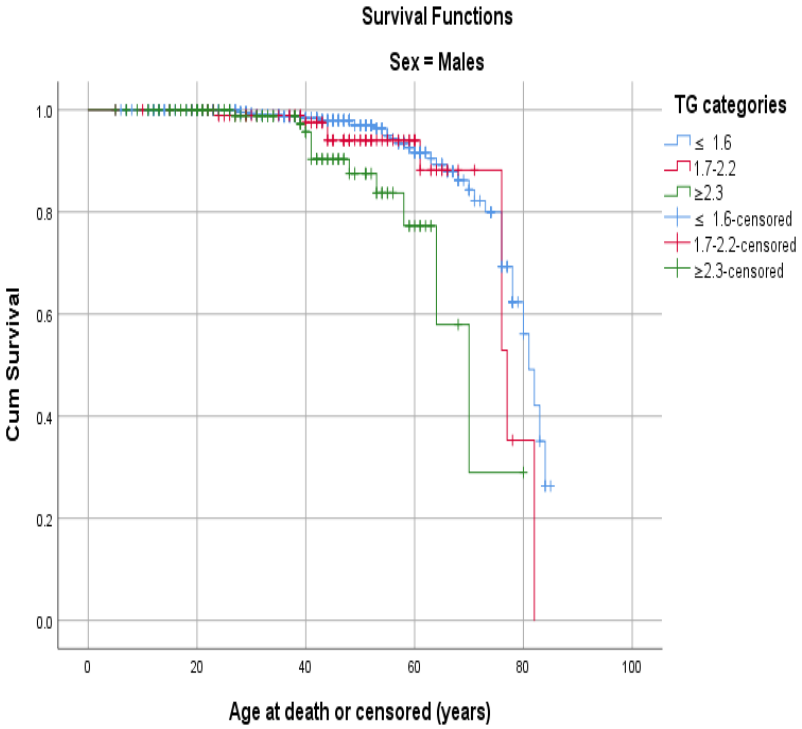


Figure 4.66: Survival curve for males with T1D in the Wirral, according to their serum TG levels (mmol/l)

For total cholesterol, the highest predictive risk of mortality was recorded in those with levels of 4.6 – 5.2 mmol/l having HR of 0.360 [95% CI: 0.002- 53.117]. Figures 4.67 and 4.68 show the survival curves for females and males relating to their cholesterol levels.

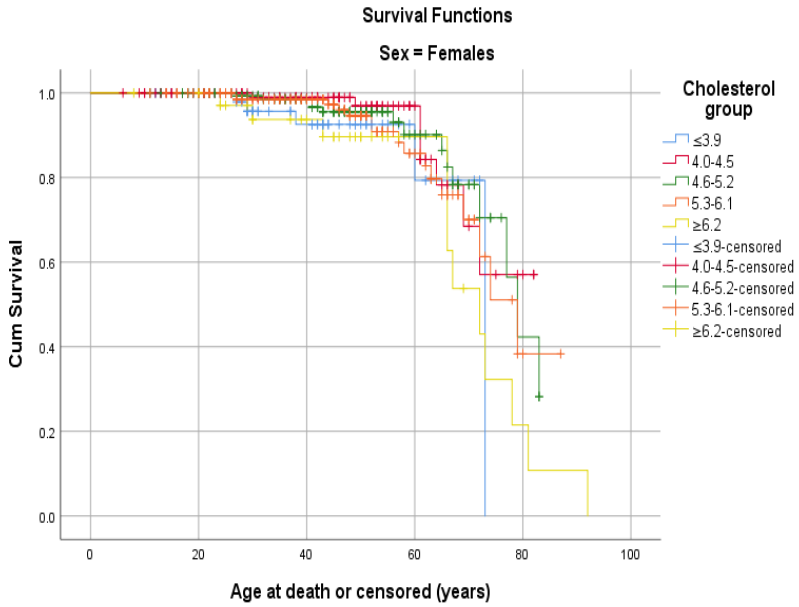


Figure 4.67: Survival curve for females with T1D in the Wirral, according to their serum total Cholesterol levels (mmol/l)

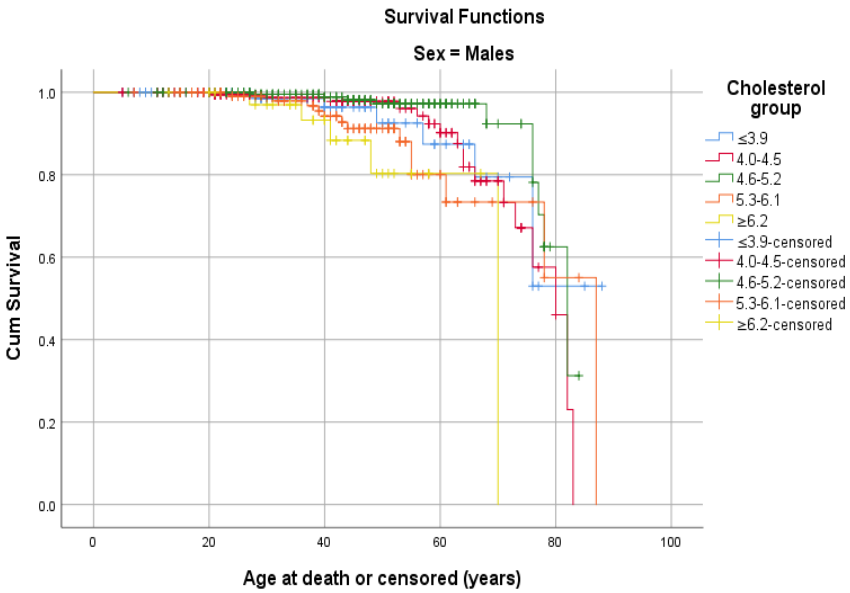


Figure 4.68: Survival curve for males with T1D in the Wirral, according to their serum total Cholesterol levels (mmol/l)

TC: HDL and LDL: HDL was not predictive of the probability of death, they were not statistically significant. Figures 4.69, 4.70, 4.71, and 4.72 show survival curves for females and males according to their TC: HDL and LDL: HDL ratios.

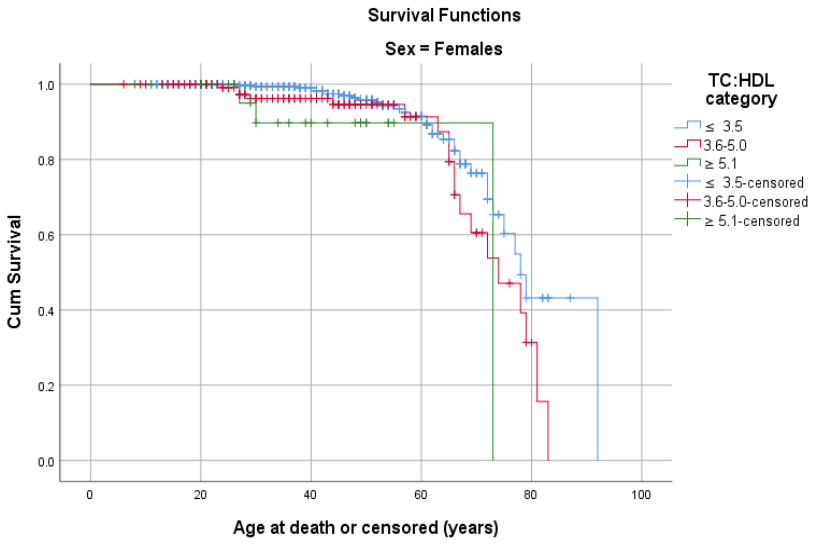


Figure 4.69: Survival curve for females with T1D in the Wirral, according to their TC: HDL ratio

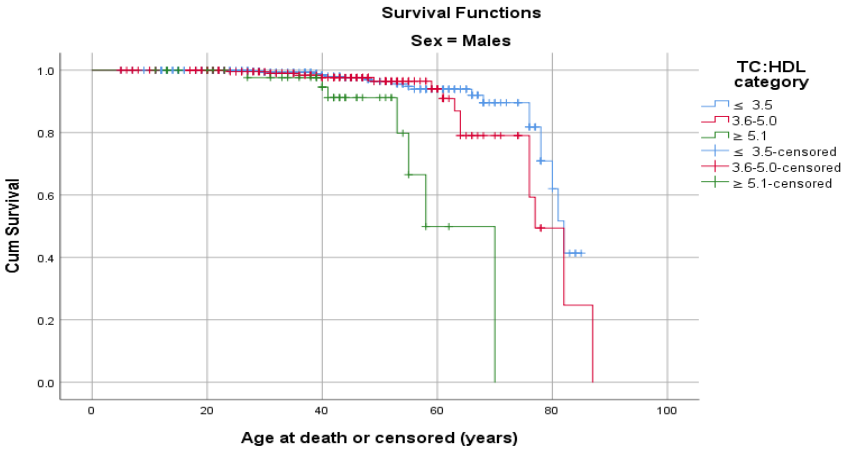


Figure 4.70: Survival curve for males with T1D in the Wirral, according to their TC: HDL ratio

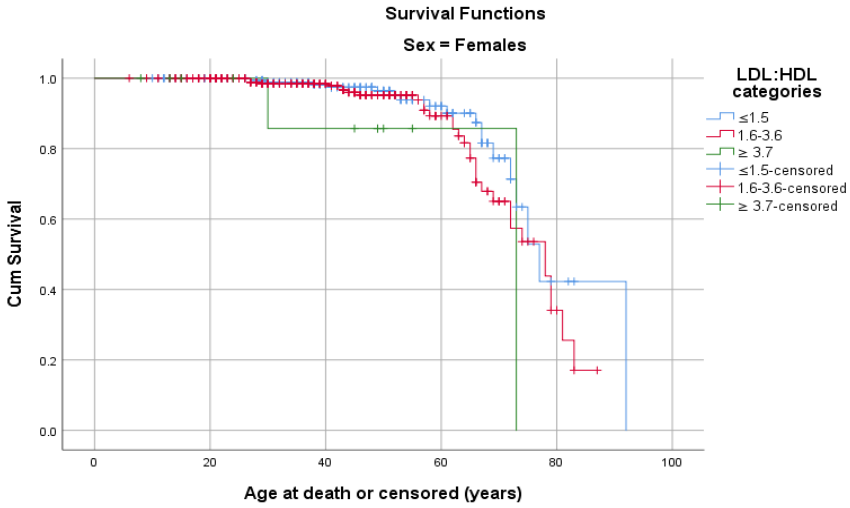


Figure 4.71: Survival curve for males with T1D in the Wirral, according to their HDL: LDL ratio

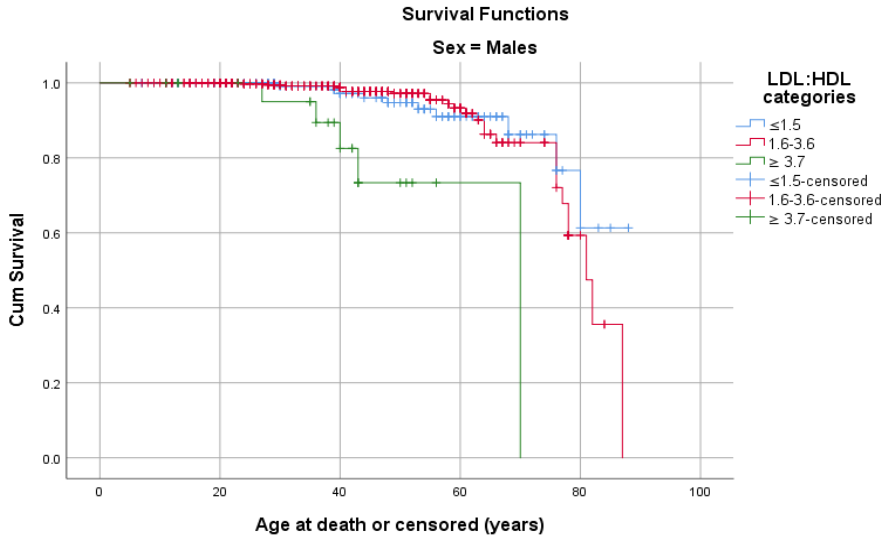


Figure 4.72: Survival curve for males with T1D in the Wirral, according to their HDL: LDL ratio

4.11 Life expectancy

Using life table analysis to estimate survival, the life expectancy for those with T1D in the Wirral, from birth was 51.17 years and 36.12 years for females and males respectively in the year 2011. Table 4.26 shows the breakdown of life expectancy extrapolated from life tables in males and females. Computation of life expectancy followed a sinusoidal pattern in life expectancy as the age of diagnosis increased. This is reflected in Figure 4.73

Table 4.24: Life expectancy (years) by age and sex in people with T1D in the Wirral 2000-2012

Age at diagnosis (years)	Life expectancy in people with T1D in the Wirral (years)	
	Females	Males
1	51.17	36.12
2	48.16	51.17
3	45.15	64.72
4	63.21	51.17
5	57.19	59.70
6	63.21	66.22
7	66.22	76.76
8	51.17	57.19
9	63.21	75.25
10	69.23	57.19
11	76.04	64.58
12	64.56	60.20
13	75.25	75.25
14	54.18	62.61
15	81.27	66.22
16	76.00	72.24
17	69.23	75.68

18	66.22	78.26
19	66.22	63.21
20	66.22	79.52
21	72.24	81.27
22	75.25	76.64
23	73.40	75.25
24	75.64	66.22
25	72.24	77.48
26	70.02	75.25
27	80.77	63.21
28	72.24	81.27
29	71.94	75.25
30	81.27	81.27
31	63.21	81.27
32	63.21	80.73
33	60.20	72.24
34	69.23	56.76
35	70.73	72.02
36	64.72	81.27
37	80.87	63.21
38	73.75	77.21
39	81.27	81.27
40	66.22	78.26

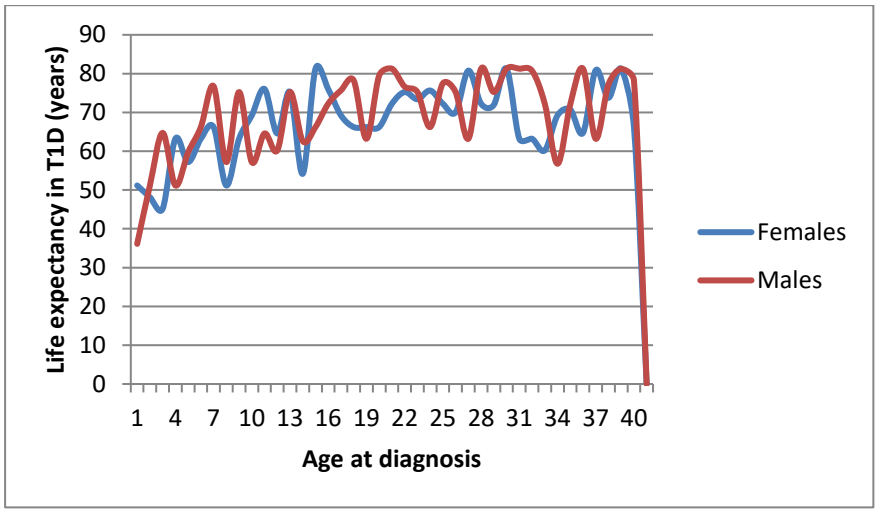


Figure 4.73: Comparative analysis of life expectancy between females and males with T1D.

Diagnosis at 5 years of age showed slightly higher life expectancy for males than females with a median survival of 59.70 years and 57.19 years respectively. A female diagnosed at the age of 10 years was expected to 12 years more than her male counterpart diagnosed at the same age.

During the teenage years, females had higher life expectancy except in the following years 14, 17, and 18. Life expectancy was equal in males and females at the age of 30 years. However,

by age 40, males diagnosed were expected to live more than females by 12 years. By comparison, to the Wirral standard population, for 2009-2011, life expectancy at birth was 77.5 years and 81.5 years for males and females respectively. This showed a difference of 30 years and 41 years for females and males respectively.

4.12 Years of potential life lost (YPLL)

Years of potential life lost (YPLL) which is a measure of premature mortality shows that males and females had 1797 years and 1553 years respectively in potential years lost. Further differentiation into YPLL rates, showed that the overall rate for T1D population was 4.8 per 1000, 4.7 per 1000 in males and 2.3 per 1000 in females. As such, males had a greater burden of almost 54% as compared to 46% in females.

Table 4.25: Sex differentiation of YPLL, YPLL (%), YPLL rate and AYPLL in T1D.

Sex	YPLL (%)	YPLL rate (per 1000)	AYPLL
Males	1797(53.6)	4.7	21.1
Females	1553(46.4)	2.3	20.2
Total	3350(100)	4.8	20.7

AYPLL, which is a weighted average to determine the magnitude of premature mortality, highlighted that males died on average 21.1 years as compared to 20.2 years in females and 20.7 years in the total T1D population.

4.13 Assessment of retinopathy

As a measure of the development of microvascular complications, retinopathy was assessed. 1224 participants were assessed for retinopathy, below is a distribution of retinopathy in T1D.

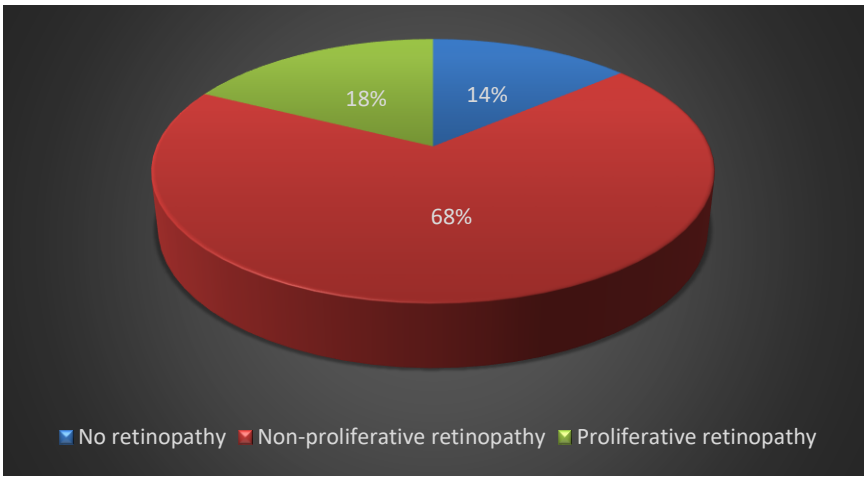


Figure 4.74: Distribution of retinopathy among T1D in the Wirral

Chapter 5: Discussion

This study investigated the predictive factors for mortality in a cohort of T1D patients in the Wirral Peninsular identified by the diabetes mellitus register between 1st of January, 2000 and 31st December, 2012. It provides an insight into factors that predict mortality in T1D. The design and analysis involved in this study's approach enabled the influx of causal associations related to mortality, predictors of mortality, survival and life expectancy in T1D. This allowed for current information with regards to certain competing risk/predictive factors such as: the age at diagnosis, gender, duration of diabetes, biochemical parameters (serum creatinine, glycaemic levels estimated from HbA1c, TSH levels, and lipid levels), smoking, blood pressure, BMI, IMD, retinopathy and cause of mortality in the cohort with T1D. The theoretical basis of this study employed the use of multiple regression analysis to identify significant predictors of mortality in this cohort.

The literature review identified that T1D accounts for between 5 – 10% of the total number of people with diabetes, with variations in the incidence and prevalence of this condition. The estimates for incidence of T1D in the UK was high at 22.8 per 100,000, this study found lower values for the incidence of T1D in the Wirral with values ranging from 2.18 – 15 per 100, 000 over the follow up period. Prevalence estimates obtained from the Wirral for T1D was between 10.9 – 116 per 100,000, these values were lower but comparable to the value obtained for the UK of 187.7 per 100,000 (JDRF, 2017). For the incidence rate, while the observed rate for this study followed a fluctuating pattern but gradual reduction at the tail end of the study, this differs from what was obtained in the UK which was a consistent yearly rise (4%) in the incidence of T1D. However, a steady rise was noted in the prevalence over the study follow up period. A similar trend is observed by the steady increase in the prevalence of T1D from other studies (Diabetes UK, 2016). For this study, the peak age at diagnosis was 10 – 14 years which does not differ from estimates obtained for the UK (Diabetes UK, 2014; Diabetes UK, 2017). This study highlighted that the growing burden of T1D is mainly due the prevalence of T1D, the reason for this trend is not fully understood however several authors point to a poor understanding of the complex interplay of genetic and environmental factors. There is need for more research to get a better understanding of the genetic and environmental triggers of the onset of T1D (Rewers & Ludvigsson, 2016; Snouffer, 2017; Mayer-Davis et al. 2017).

This study identified malignancy-related deaths (21.6%) as the major contributor to mortality in this cohort. This is in contrast to findings from other studies which attribute the major cause of death in T1D to cardiovascular diseases (Tu et al. 2008; Huxley et al. 2015; Lind et al. 2015).

However, in this cohort, cardiovascular diseases still account for a high proportion of mortality (16.2%). In this study cerebrovascular disease has been allocated a separate group however, in various other studies it has been included as one of the cardiovascular diseases (Lind et al. 2011; Miki et al. 2013); following this principle, cardiovascular complications will account for approximately 30% of deaths making it to account for the most amounts of deaths in this cohort (Huxley et al. 2015).

In this study, significant predictors of mortality in this cohort (p-value <0.05) were the age at diagnosis, duration of diagnosis, HbA1c, SBP, DBP, and triglyceride (TG) levels. The findings from this study agree with some of the risk factors identified from previous studies (Soedamah-Muthu et al. 2008, 2014; Olson et al. 2002; Weis et al. 2001; Mühlhauser et al., 2000).

These findings support the argument that to limit the impact of T1D on premature mortality, measures should be focussed on limiting the effects of cardiovascular complications by enhancing measures that reduce modifiable cardiovascular complications (Mameli et al. 2015). As such one of the cardinal measures for the prevention of cardiovascular complications in T1D is optimal glycaemic control. This is observed by the concept of "Metabolic Memory" which entails the introduction of early aggressive treatment with the aim of establishing normal metabolic control at an early stage of the condition which helps to limit cardiovascular complications (Misra, & Bloomgarden, 2018; Testa et al. 2017). This concept was supported by the DCC/EDIC trial which established that those in the intensive therapy group had reduced rates of retinopathy, nephropathy and CVD (Lachin et al. 2014; Lachin et al. 2016). However, there is a need to further explore certain scenarios in the management of T1D such as whether variations in glycaemic levels affect the concept of metabolic memory and at what point during the life cycle of the T1D is there optimum effect of intensive care in management either at the early stages or the later stages of control (Misra, & Bloomgarden, 2018). This study also identified hypoglycaemia as posing significant mortality risk; this is evident through repeated hypoglycaemic episodes and with increasing duration of T1D, there is an increased chance of reduced hypoglycaemic awareness which is a predictor of mortality (Rewers et al. 2002). Additionally, repeated hypoglycaemic episodes have been considered as possible initiating factor in the development of preclinical atherosclerosis, the mechanism of which remains poorly understood (Giménez et al. 2011). The quality statement provided by NICE Quality standard [QS125] is focussed on providing CSII with CGMs to individuals with T1D prone to repeated severe hypoglycaemic episodes and reduced hypoglycaemic awareness. The use of CGMs and CSII, if applied properly have been found to enhance better glycaemic control while

reducing hypoglycaemic episodes and mitigating long term CVD complications (Sherr et al. 2018; Lung et al. 2014; Boland et al. 1999). In the future, with further technology advancement and reduce cost of production, there may be a need for cost benefit analysis to introduce these technologies as standard measures of care.

This study identified triglycerides as a significant predictor of mortality in T1D, elevated TG has been found to closely correlate with microalbuminuria and the progress of chronic renal failure in patients with long term T1D (Mäkinen et al. 2012). Research has also established dyslipidaemia as increasing the risk of developing CVD, a potent risk factor for all-cause mortality in T1D (Collier et al. 2018). Dyslipidaemia is identified as presenting increased risk of poorer glycaemic control, nephropathy and hypertension (Zabeen et al. 2018; Vergès, 2009). In T1D, it is characterised by both quantitative and qualitative changes in lipid levels (Ganjali et al. 2017), this implies that to achieve optimal control in T1D, a multipronged approach is required to tackle the multifactorial risk factors in T1D. One approach is the use of statin therapy for lowering lipids which has been found to be beneficial for improved outcomes (Hero et al. 2016), but the NICE guidelines advocates its use in T1D for patients over the age of 40 years, established nephropathy and T1D duration > 10 years (NG17, NICE, 2015a). In this study, it could be inferred that CYPs are also prone to abnormal lipid levels at an early stage and thus prone to early onset of CVDs. As such, this finding supports the argument by some authors that further research is needed to explore the beneficial use of statins in lowering abnormal lipids starting from adolescent age (Marcovecchio et al. 2017; Canas et al. 2015). Similarly, the use of use of ACE-I which has beneficial effects in reducing the incidence of microalbuminuria and hence improving outcomes is not advocated in CYPs, further research is needed to explore their efficacy and safety in the young with T1D (Marcovecchio et al. 2017; Donaghue et al. 2014). This study also found blood pressure to be significant predictor of mortality, because the use of medications is not encouraged by the NICE in CYPs, this implies that further emphasis should be placed on lifestyle measures to improve outcomes. One of such measures advocated by the NICE guidelines is the use of screening methods to identify and follow up micro-and macrovascular complications. The guidelines advice the start of screening for nephropathy and retinopathy from the age of 12 years, this is to identify at an early stage those at risk of early complications (NG18, NICE 2015b). During the teenage age years and early in the diagnosis of diabetes, further emphasis should be placed on structured education and lifestyle modification such as diet and exercise. Structured education applied at an early stage is found to enable the individual diagnosed with T1D to better understand their condition.

The acquired knowledge enhances patient empowerment by providing them with the necessary skills and motivation to better manage T1D. Hence an empowered individual is more likely to experience better medical, social and behavioural outcomes. This results in cost effective use of available health resources (Chatterjee et al 2017). Recent evidence support the hypothesis that exercise significantly reduces the risk of premature mortality in T1D (Tikkanen-Dolenc et al. 2017), research also highlighted that exercise has the beneficial effect of increasing insulin sensitivity, with a further effect of better glycaemic control (Bernardini et al. 2004).

In this study, the peak age of diagnosis was 10-14 years; this implies that this age group is very important for targeted intervention. In gleaning from the studies conducted by Mabhala et al. (2017, 2018) which argues that maladjusted individuals with negatively altered life course are usually influenced in early life possibly from teenage years into early adulthood and is familial and societal context specific. This view is further supported by Worthman, Tomlinson, & Rotheram-Borus, (2016), who suggested that the maximal influence of parenting on any child occurred during the adolescent years (10 – 15 years [median 12 years]). They argued that this is the period where the child is most at risk of several influences (familial and societal) that threaten their educational, health, and social attainment, a derailment of which may have enduring consequences for lifetime well-being. Additionally, the pubertal period raises its own risk of physical, psychological and behavioural (peer pressure) influences that could either enhance resilience or deviate one's life course (Blakemore & Mills, 2014). As argued by Spencer et al. (2012), the key to successful outcomes in the management of T1D are strong family cohesion and societal support. This is supported by Ashraff, Siddiqui, & Carline, (2013), who argue that management of T1D in a child impacts on family life and young people who reported optimal control were more likely to be from family units that supported independence and had strong family cohesion and less conflicts. There is need to explore interventions that target family relationships with the aim of enhancing communication, improving conflict resolution, and enhancing resilience to create a balanced family atmosphere which has the potential to improve adherence to treatment regimens and self-care (Hauser et al. 1990; Wysocki et al. 2006, 2007). One of such intervention is the Behavioural family systems therapy (BFST-D) on diabetes implemented in the US that found significant adherence to treatment regimens and improvement to family cohesion (Wysocki et al. 2007). There is need for further research to replicate this intervention or similar variants in cohorts of T1D in the UK (Funnell, 2006). The teenage years are also noted as a period of social influence from friends and peers; they are noted to be part of the support networks that are important in the management of T1D.

Few studies have noted that support from friends and family create an atmosphere of resilience (Ashraff, Siddiqui, & Carline, 2013). However, there is need for further research to explore the influence of peers and how these can be integrated into models of care for T1D (Akhter, Turnbull, & Simmon, 2018; Kazemi et al. 2016; Palladino, & Helgeson, 2012).Additionally, the benefits of the influence of support networks can be further enhanced by structured education, this is evidenced by the impact of several educational programmes in T1D (Plank et al. 2004; Davies et al. 2008; Deakin et al. 2006, 2011; Diabetes UK, 2015, X-PERT, 2017; NICE, 2016a).

This study noted adverse mortality outcomes for those in the lower socioeconomic groups, although this finding should be viewed with caution and requires further research, it infers that social and economic conditions in which these patients resides can impact on their (both patients and caregivers) ability to adequately manage T1D to achieve optimum control (Mabhala et al. 2017, 2018; Worthman et al. 2016; De Bellis, & Zisk, 2014). This translates to imply that for policy enactment and implementation, there is need to enact policies which support families (care givers) and patients with T1D especially during their teenage years. These policies should focus on identifying those most vulnerable to the impacts of adverse societal and environmental factors with the aim of ensuring equitable resource availability and building resilience that positively impacts on treatment adherence and glycaemic control in T1D (Neckerman et al. 2016; Worthman et al. 2016).

This study revealed the absolute risk of mortality varied according to the predictor variable being examined. The evaluation of these predictor variables is found to reveal that the exact contribution of a predictor variable to mortality risk fall within a continuum. It is important to interpret these findings based on a balanced view of the impact of these variables. Several studies on T1D highlight the influence several predictor variables on mortality risk at varying points of exposure status to the condition (Distiller, 2014; Schoenaker et al. 2014; Grau et al. 2016; Lachin et al. 2016). This study highlight that these multiple risk factors do not only present as singular risk factors to mortality but are also cumulative in complex interactive processes (Distiller, 2014). Research suggests that while some of the predictive risk factors can be prevented or potentially reversible other are irrevocable. In this study, some of the irrevocable risk factors are age and gender; some potentially revocable risk factors were blood pressure, lipid profiles, and glycaemic control.

This study has highlighted differential increased potential risk of mortality according to gender. This study showed that females were 4 times at increased risk of mortality when compared to their males' counterparts. This finding is in agreement with the study carried out by Huxley and colleagues who reported similar results (rSMR 1·37 [95% CI 1·21–1·56] p<0·0001) and also Lung et al. (2014) who reported that males had a RR of 3.25 (95% CI 2.82–3.73) as compared to females with RR of 4.54 (95% CI 3.79–5.45). Although the reason behind this trend remains uncertain, a possible explanation for this observation is explained by Huxley, Barzi, & Woodward, (2006). They suggest that effects from vascular dysfunction of this condition such as coronary artery calcification and endothelial damage are more pronounced in females than males. One other reason suggested is that women, in general, have a higher life expectancy that than men, hence they are prone to the longer exposure of the cumulative effect of glycaemic variations that is hypo and hyper-glycaemia (Huxley, Barzi, & Woodward, 2006). Several other authors have suggested other reasons for this trend; they suggest that women due to their physiological attributes may influence the effect of insulin sensitivity leading to the observed trend. Some of these factors include inputs from the endocrine pathways (hypothalamus-pituitary-ovarian axis), and hormonal factors associated with the effects of puberty and menopause (Kim, Elimi, Henderson, Cogen, & Kaplowitz, 2012; Kaplowitz, 2012; Paris et al., 2009; Amiel et al., 1986; Huxley, Peters, Mishra & Woodward, 2015). This trend is also noted due to significant excess risk of mortality identified in females secondary to cardiovascular disease hence increasing the cumulative effect of several risk factors in women (Rawshani et al. 2018). The absolute risk of mortality within the study period revolved around a narrow range of 3% to 5%. The maximal risk of mortality in the study was in 2005 with a maximal risk of 5%; this could be attributed to coincide with the early transition period that indicated the implementation of the National service framework (NSF) for diabetes (Diabetes UK, 2008). The overall risk of mortality during the study period fell to 2%; this reflects developments in the better management approaches of several risk factors of T1D.

This study found out that the age of diagnosis, and increasing duration of diabetes, was significantly associated with increased risk of mortality. Although this study identified relatively reduced mortality risk before the age of 18 years, the relative risk of mortality significant increases after the age of 18 years. The reasons for this observed trend may be due indirectly to the cumulative impact of the effects of metabolic syndrome. A study by Chillarón et al. (2010) identified the incidence of metabolic syndrome in 31.9% of their cohort diagnosed after the age of 18 years. They also found out that age at diagnosis was a significant and

independent risk for the development of metabolic syndrome. They also suggested an increased association of metabolic syndrome with the early onset of microvascular complications. A further study by Chillarón et al. (2014) argued that between 8 – 40 % of individuals diagnosed with T1D after the age of 18 years meet the criteria for metabolic syndrome. Metabolic syndrome was linked to the early onset of cardiovascular diseases which was identified as one of the leading causes of mortality in T1D (Chillarón et al. 2015). Another possible reason to explain this trend may be the resultant effect of reduced β-cell mass with increasing age as observed by reduced detectable levels of IAA with increasing age and dysfunctional mitochondrial function with increasing age (Chen et al. 2017; Bluestone, Herold, & Eisenbarth, 2010; Akirav, Kushner, & Herold, 2008; Matveyenko, & Butler, 2008). Hence the link between increasing age of diagnosis with increased mortality may be as a result of complex interactions of multifactorial factors.

This study outcome reflects a significant increase in mortality risk with increasing duration of T1D. This highlighted a positive correlation with increasing duration of this condition which showed proportional linearity. This finding is supported by findings from the study conducted by Rawshani and colleagues in 2018 which found an increased risk of developing cardiovascular disease conditions with those diagnosed at the younger age group (1 – 10 years), with the early development of cardiovascular disease they were at an increased risk of mortality. As the duration of T1D progressed, there was an increase in the cumulative metabolic effects from cardiovascular diseases leading to excess premature mortality. This trend was further highlighted when the duration of diabetes was greater than 20 years. This study confers with findings from other studies (Akata, Mabhala, Bowen-Jones, & Cooper, 2016; Orchard, Costacou, Kretowski, & Nesto, 2006; Lung et al. 2014; Huxley, Peters, Gita, & Woodward, 2015).

For this study glycaemic control is shown to carry a significant risk of mortality. This study showed that the maximum risk of mortality was observed in those with average HbA1c levels at ≤ 5.9% (41mmol/mol) at 25%. This study highlighted nonlinearity similar to a U-shaped pattern with spline knot points at HbA1c levels (7.5%, 8.5%, 9.5% and 10.1%). The least risk of mortality was found in those with HbA1c levels of 6.0-6.4% (42-46mmol/mol). Above HbA1c levels of 6.5%, mortality risk followed a varied sinusoidal pattern (figure 4.3f). This study concurs with findings for Schoenaker et al. (2014) who observed a similar trend with glycaemic control and mortality. Alternative a study by Lind et al. (2014) identified a monotonic linear rise in the risk of mortality with a corresponding increase in average HbA_{1c}

levels. The possible reasons that explain the observed trend in this study remain uncertain. However some authors argue that individuals with lower HbA1c levels are at an increased risk of hypoglycaemic coma hence increased risk of mortality. This is especially evident with increasing duration of T1D when there is an increased loss of hypoglycaemic awareness (Lachin et al. 2016). There may also be a significant contribution to higher mortality risk from death in bed syndrome which is very difficult to evaluate (Secrest et al. 2011). Several other contributing factors are noted to have contributions to increased hypoglycaemic levels such as the presence of concurrent clinical conditions such as anaemia or conditions with increased haemoglobin turnover, hypokalaemia, QT syndrome, renal failure, poor compliance with treatment regimens, psychiatric disorders, poor cognitive impairment, and social problems (Lind et al. 2016; Tsujimoto et al. 2014; Riddle et al. 2010; Gallagher, Le Roith, & Bloomgarden, 2009).

Smoking is acknowledged to be one of the principal risk factors for the cardiovascular disease, coronary heart disease, peripheral arterial disease, heart failure and all-cause mortality (Pan et al. 2015; Weis et al. 2001). The findings from this study show that the absolute risk of mortality was 7%, 8%, and 14% in non-smokers, smokers, and ex-smokers respectively. Smoking had a HR of 1.241 [95% CI 0.606- 2.540] and p-value 0.556. These results agree with findings from Pan et al. 2015). Factors that may influence higher mortality risk in ex-smokers than current smoker include the number of years, quantity smoked and time of quitting which were not explored for this study.

This study noted the increased relative risk of mortality in quintile 1 (most deprived), and quintile 4 (below average). This indicates that the construct of IMD increases the risk of mortality in T1D. However the results were not statistically significant. Findings from this study confer with findings from several other studies (Scott et al. 2017; Saydah, Imperatore, & Beckles, 2013; Forssas et al. 2012; Secrest et al. 2011).

This study showed an increased risk of mortality with BMI 35.0 - 39.9 Kg/m2 and $\geq$ 40 kg/m2 having respective HR of 1.479 [95% CI: 0.013- 162.753] and 1.352 [95% CI: 0.004- 437.779] although not statistically significant. The absolute risk for these 2 groups were 19% and 20% respectively. The findings from this study reveal almost a J shaped pattern of mortality, a phenomenon similarly identified from other studies termed the obesity paradox (Carnethon, Rasmussen-Torvik, & Palaniappan, 2018; Qin, Liu, & Wan, 2017; Conway et al. 2009). Although some studies do not record any significant relationship of BMI with mortality in T1D,

obesity is noted to be a risk factor in the development of cardiovascular disease hence an indirect risk to increase mortality in T1D (Vestberg et al. 2018).

This study highlighted that worsen levels of serum creatinine significantly increased the risk of mortality. This pattern reflected a linear proportionality to mortality risk with absolute risk for 107-129μmol/l, 130-149μmol/l, and ≥ 150μmol/l, of 18%, 40%, and 40% with a relative risk of 3.0, 6.7, and 6.7 respectively. This study highlights that nephropathy and its progression to chronic kidney disease and end-stage renal failure still present a significant risk of mortality in T1D. Nephropathy is also noted to be strongly associated with the onset of cardiovascular disease through its cumulative but varied mechanisms which enhance vascular damage (de Ferranti et al. 2014). The study agrees with similar findings from several other studies and emphasises the need for reno-protective measures to mitigate the long term impact of nephropathy (H. de Boer, & Bakris, 2018; Gagnum et al. 2017; Lind et al. 2014; Bentata et al. 2013).

5.1.The relationship between various predicting risk factors and mortality in T1D

This study found a linear rise in the risk of mortality with increasing systolic blood pressure (SBP). The absolute risk of mortality was highest (35%) in those who had SBP ≥160mmHg. The relative risk also revealed a similar pattern to absolute risk as those with SBP ≥160mmHg had a relative risk of 11.6. Values of 140 – 159mmHg also showed an increased risk of mortality of 23%. The HR documented for all-cause mortality as it relates to SBP was 1.666 [95% CI: 0.669 – 4.149], p-value 0.273. The findings in this study are consistent with findings from other studies as the advent of raised blood pressure is shown to precipitate and exacerbate the clinical course of micro - and macrovascular complications (Collier et al. 2018; Perkins et al.2003; Orchard et al. 2001; Weiss et al. 2001). This study showed that the risk of mortality was prevalent at the two extremes of diastolic blood pressure. This reflected a U-shaped pattern with those having blood pressures ≤59 mmHg and ≥100mmHg having absolute mortality of 38% and 35% respectively. The HR documented for all-cause mortality as it relates to DBP was 1.105 [95% CI: 0.414 – 2.953], p-value 0.842. This result was in agreement with observations from other studies (Collier et al. 2018; Perkins et al.2003; Orchard et al. 2001; Weiss et al. 2001).

Abnormal lipid profiles remain potent predictors of the advent of cardiovascular disease and total mortality in T1D (Weiss et al. 2001; Orchard et al. 2001). For total cholesterol (TC) levels, this study found an increase in the risk of mortality with increasing levels of TC. This was

particularly evident with levels of ≥6.2mmol/l which had a mortality risk of 24%, findings from this study are consistent to findings from other studies (Schofield et al. 2016; Maahs et al. 2010; Pietri et al. 1983).

This study also found an inverse V-shaped relationship in mortality risk with the rise in total triglyceride levels (TG). The maximal risk of mortality was found in those with TG levels 1.7-2.2mmol/l with 12% absolute risk of mortality. Although the risk mortality in those with TG levels of ≥2.3mmol/l was marginally increased with 10% absolute risk of mortality, this finding was significant, with HR for all-cause mortality was 1.286 [95% CI: 0.545- 3.036], P-value 0.566. The findings from this study contrast with findings from other studies which show a direct linear rise in the risk of mortality with rising TG levels (Gylling et al. 2004).

This study highlighted a proportionate increase in mortality risk with increasing LDL levels. The highest risk of mortality was found in those with LDL levels ≥ 5.0mmol/l with an absolute risk of 27% and relative risk of 5.4. These findings agree with findings from other studies (Olesen et al. 2017; Schofield et al. 2016; Di Angelantonio et al. 2009).

In this study, an increase in HDL levels was associated with an increase in the risk of mortality; those with HDL levels of ≥ 1.6mmol/l had the highest risk of mortality of 8%. However, this observation contrasts with findings from other studies. (Hewing, Moore, & Fisher, 2012; Voight et al. 2012; Emerging Risk Factors Collaboration et al. 2009). Early and later studies such as the Framingham study that examined the relationship between lipid profiles and cardiovascular risk suggest that higher levels of HDL confer protection against the advent and progression of cardiovascular diseases. This is achieved through its antiatherogenic effects on vascular function (Ganjali et al. 2017; Arca et al. 2007; Gordon et al. 1977). The study by Bain et al. (2003) suggests elevated HDL levels may confer some level of protection in T1D patients, which is enhanced by genetic predisposition. However, findings in this study do not reflect this; a possible reason for this observation is put forward by a recent study by Femlak and colleagues in 2017. They suggest that although in the general population, raised HDL levels independently confers risk reduction to alter the progress of cardiovascular disease; this is no present in the pathological state of T1D. In T1D, these functions of HDL become dysfunctional. They suggest that possible reason for this is an alteration of the HDL proteome, which then becomes a proinflammatory protein, following oxidative insults to enzymatic activities associated with the functions of HDL. This subsequently leads to a deficiency in the ability of HDL to suppress inflammatory signals in T1D. Another mechanism that explains the findings

of this study may be due to genetic alteration to the HDL molecule which impacts on its quality. This, therefore, means that raised quantity of plasma HDL-C does not necessarily confer protection from cardiovascular disease (Eren, Yilmaz, & Aydin, 2012 Costacou, Evans, & Orchard, 2011: Vergès, 2009).

For TC/HDL ratio and LDL: HDL ratio, this study identified trends where increased levels of cholesterol ratios reflected an increased risk of mortality. For TC/HDL ratio, values ≥ 3.7 had an absolute risk of 19% and relative risk of 2.7, TC/HDL ratio with values ≥ 5.1 had an absolute risk of 13% and relative risk of 2.2. The HRs for TC/HDL and LDL/HDL ratios were 1.615 [95% CI: 0.643 - 4.053], p-value 0.308 and 1.465 [95% CI: 0.598 - 3.591], p-value 0.403. Findings from this study are consistent with findings from other studies (Guy et al. 2009; Gylling et al. 2004).

Research has highlighted an increased risk of thyroid dysfunction with T1D (Umpierrez et al. 2003), with a stronger correlation for hypothyroidism. The study revealed a U-shaped pattern in mortality risk with T1D according to TSH levels. The mortality risk was more prominent with TSH levels of ≤0.4 mU/L, having an absolute mortality risk of 15% as compared with TSH levels ≥4.0 mU/L, having an absolute mortality risk of 12%. The findings from this study should be interpreted with caution as there is paucity of research that links thyroid disorder with mortality risk in T1D. Also findings from this study are based on a small number of participants inferring reduced statistical power to ascertain such causality and effect. However research findings only correlate the increased incidence of hypothyroidism to T1D and increased severity of T1D in those having hypothyroidism, there is need for further research to identify any correlations between mortality and thyroid disorders in T1D (Jonsdottir et al. 2017; Fatourechi et al. 2017).

5.2.Evaluation of mortality rates and standardised mortality rates

Limited research has been done to evaluate the cause of mortality, trends in mortality, survival in a population cohort of participants with T1D in the Wirral, UK. This elaborates specific estimates on these trends.

This study provides precise estimates of age – and sex-specific mortality rates, and absolute mortality. In the study, revealed varied patterns mortality with age and sex specific (adjusted and standardised) rates. The age – and sex-specific mortality rates found higher specific mortality rates in males for age groups 0-4, 15-19, and 30-34; females had higher specific mortality rates in age groups 5-9, 10-14, 20-24, 25-29, and 35-39 years. The difference in

specific mortality rates was marked in the age group 35-39 where there was a fourfold difference in rates between females and males. These patterns are reflected in the age-adjusted and standardised age-adjusted mortality rates. However, in contrast to Laing et al. (2003) who found similar mortality rates for age groups in males and females below the age of 40 years. The mortality rate difference estimates obtained from this cohort reveal negative values which show that age-adjusted mortality rates for this cohort were higher than those obtained from the standard Wirral population. This reflects excess mortality in this cohort as compared to the standard population. The findings from this study agree with the trends observed in the study by Laing and colleagues in 2003.

The specific mortality rates according to calendar year were higher in females than males reflecting similar trends in adjusted and standardized adjusted mortality rates. These findings reflect similar findings in other studies (Soedamah-Muthu at al. 2006; Skrivarhaug et al. 2006; Morrish et al. 2001).

This study found a sinusoidal pattern of standardised mortality ratio (SMR) according to age groups, the highest SMR was recorded in the age group 5-9 years with SMR 8.05 [95% CI: 2.07 -14.03]. The lowest SMR was recorded in the age group 35-39 years with SMR 6.73 [95% CI: 3.2 – 10.26]. Across all age groups, this study found almost similar SMRs in both males and female participants. This result agrees with several other studies (Gagnum et al. 2015; Nishimura et al. 2001). However, several other studies show higher SMRs for females than males. A study by Laing et al. (1999), found SMRs of 2.7 (95% CI 2.5–2.9) and 4.0 (95% CI 3.6–4.4), in males and females. Harjutsalo, Forsblom, & Groop, (2011) estimated higher SMRs for females than males in their population cohorts with values of 5.5 for females as compared to 3.0 in males for the early onset cohort, and 3.6 for females as compared to 2.6 in males for the late onset cohort. These differences may be attributed to the population characteristics of the comparative cohorts.

5.3.Predictor variables and their influence on T1D with survival, life expectancy and potential years lost.

Previous studies have established reduced life expectancy with T1D with the expected reduction in years ranging from 12 to 17 years (Livingstone et al. 2015; Brown, Scott, & Moir, 2001). The reduction in life expectancy is attributed to the impact of microvascular and cardiovascular complications n T1D (Liang et al. 2001).

Using life table analysis, this study found reduced life expectancy from birth with having a diagnosis of T1D. Analysis of this cohort showed that females from birth were expected to live to the age of 51 years while males from birth were expected to live to the age of 36 years. With life expectancy from birth in the Wirral for males and females being 78 and 82 years respectively, this reflected a reduction of 31 years for females and 42 years in males. At age 40 years, females and males were expected to live to ages 66 and 78 years respectively. This study reflects similar patterns observed from previous studies (Livingstone et al. 2015; Brown, Scott, & Moir, 2001).

This study found no significant relationship between gender and survival, the survival period for males and females were 77.185 years [95% CI: 75.191 – 79.179] and 76.011 years [95% CI: 73.169 – 78.000] respectively. The real impact of the burden of T1D is reflected in the burden of premature mortality as evidenced by the YPLL, for males and females having 1169 and 1005 potential lost years respectively. Cardiovascular risk factors are identified as contributory to lost years (Livingstone et al. 2015; Brown, Scott, & Moir, 2001).

This study found that age at diagnosis was an important determinant of survival, although not statistically significant, this study found a mild increase with survival times as age of diagnosis increased, however, the absolute risk of mortality increased with increasing age of diagnosis. The results from this study are comparable to results from other studies (Rawshani et al. 2018)

This study found the increasing risk of mortality with increasing duration of diabetes. However, survival with T1D followed a sinusoidal but linear rising pattern with increasing duration of diabetes. Significantly, those with duration of diabetes less than 10 years had median survival for males and females of 48.416 years [95% CI: 47.625 – 49.207] and 45.527 years [95% CI: 42.961 – 48.094] respectively. This indicates that there was better survival with longer duration of diabetes. This correlates with findings from the study by Elsamahy, Elhenawy, & Altayeb, (2017) who argue that a shorter duration of diabetes may predict poor long-term outcome.

This study identified a significant relationship between glycaemic control and survival for T1D. Although survival followed a sinusoidal pattern, those with HbA1c $\leq$ 5.9 (41mmol/mol) had worsened survival times of 59.415 years [95% CI: 44.180 - 79.649], 58.286 years [95% CI: 45.040 - 93.531], 59.101 years [95% CI: 45.607 – 72.595] respectively for males, females and the total cohort respectively. This correlates closely with the finding that those with lower values for HbA1c [$\leq$ 5.9 (41mmol/mol)] has the greatest risk of mortality (Schoenaker et al. 2014).

This study identified a U-shaped pattern with survival times according to serum creatinine levels. The values obtained for this cohort were significant; this indicates that increasing creatinine levels which correlates closely with worsening renal function and advancement of diabetic nephropathy relates to reduces survival in T1D. Findings from this study correlate with findings from other studies (H. de Boer, & Bakris, 2018; Gagnum et al. 2017; Lind et al. 2014; Bentata et al. 2013)

For systolic blood pressure (SBP), although this study identified a linear increase in the risk of mortality with increasing SBP, this pattern is not reflected in the survival times. Survival times increase with the rise in SBP. The reason for this observation remains unclear. However, this finding is not statistically significant.

Diastolic blood pressure (DBP) reflected an increased risk of mortality at the two extremes of blood pressure; however, observations from survival time show significantly, that higher values for DBP (≥100mmHg) resulted in reduced survival times. This observation is consistent with findings from other studies (Collier et al. 2018; Perkins et al.2003; Orchard et al. 2001; Weiss et al. 2001). Plausible explanations for the observed pattern is that hyperglycaemia contributes to the vascular dysfunction which aids in the cascade of events that result in the formation of atherogenic plaques implicated in arterial stiffness and its precipitant effect on increased cardiovascular risk (de Boer et al. 2008).

This study identified that increased levels of HDL, TG, LDL, LDL/HDL and TC/HDL ratios were associated with increased mortality risk. These findings agree with findings from other studies (Schofield et al. 2016; Maahs et al. 2010; Pietri et al. 1983).

With regards to survival, the trend observed with total cholesterol which was statistically significant reflected fluctuations but reducing survival with increasing levels of total cholesterol. HDL levels did not reveal any particular trend, but those with HDL levels of ≥ 1.6mmol/l had survival times of 69.000 years [95% CI: 62.195 - 75.805] and 67.000 years [95% CI: 63.675 - 70.325] in males and females respectively. A linear trend was observed with TG levels were increase in TG levels lead to a reduction in survival times for this cohort. The least survival times were observed in males and females with TG levels of ≥ 2.3mmol/l having a median survival of 70 years [95% CI: 60.933 – 79.067] and 72 years [95% CI: 62.015 – 81.985] respectively. Similarly, the least survival times for LDL levels was observed in males and females with LDL levels ≥ 5.0 mmol/l having a median survival of 45 years [95% CI: 37.031 – 52.969] and 46.8 years [95% CI: 45.512 – 96.088] respectively. There was a

proportionate fall in median survival with rising levels of LDL. Survival relating to TC: HDL levels revealed an observed trend that reflected reduced median survival with rising ratios. The least median survival of 58 years [95% CI: 49.826 – 66.174] and 73 years [95% CI: 61.078 – 75.783] as observed for males and females respectively was found with TC: HDL ratios ≥ 5.1mmol/l. However, for LDL: HDL ratios, a similar trend was observed for females but not for males. These findings further add to the results of other research (Olesen et al. 2017; Schofield et al. 2016; Di Angelantonio et al. 2009; Ganjali et al. 2017; Arca et al. 2007; Gordon et al. 1977).

These observations lend credence to the argument that dyslipidaemia is one of the main factor responsible for the development of cardiovascular disease which contributes to excess mortality in T1D. There is the need to continue the mortality risk reduction measures such as the use of physical exercise, the use of statins and ACE inhibitors (Kearney et al. 2008). Furthermore, the combination of abnormal lipid profiles and increased blood pressures further increase the risk of diabetes vascular complications. (Krentz, Clough, & Byrne, 2009)

For this study, current smokers had the least survival times as compared to non-smokers and ex-smokers. The median survivals for current smokers were 75.338 years [95% CI: 71.689 – 78.987] and 69.159 years [95% CI: 62.732 – 75.589] for males and females respectively. The link between smoking and reduce survival in T1D is attributed to a range of factors. Smoking confers its harmful effect T1D through its independent risk to the development of cardiovascular disease and its effect on the increase in all-cause and excess mortality in T1D (Haire-Joshu, Glasgow, & Tibbs, 1999; Haire-Joshu, Glasgow, & Tibbs, 2004). Smoking is seen to potentiate the risk of development and progression of macrovascular and microvascular complications; this is achieved through several mechanisms (Chaturvedi, Stephenson, & Fuller, 1995). Biochemically, smoking significantly potentiates elevated levels of abnormal lipids and increases dysfunctional levels of HDL cholesterol; it also contributes to the advent and progression of insulin resistance and poorer glycaemic control (Solberg et al. 2004; Al-Delaimy et al. 2001; Facchini et al. 1992). In T1D, smoking increases the risk of worsening microvascular complications of neuropathy, retinopathy and nephropathy hence contributing to reduced survival times and worsening mortality risk (Clair et al. 2015; Biesenbach, & Zazgornik, 1996).

This study results revealed increased mortality risk with increasing BMI. Survival trend with BMI found a decreasing trend with increasing BMI. The least survival times were recorded in

males and females with BMIs 35.0 - 39.9 kg/m2 (Minges, Whittemore, & Grey, 2013; Conway et al. 2009), they were 40 years [95% CI: 22.396 - 57.604] and 61 years [95% CI: 48.998 - 73.002] respectively. These findings are consistent with results from other studies (Conway et al. 2009).

This study found no significant trend in survival according to IMDs assigned, however, mortality risk revealed J shaped pattern of mortality, these findings agree with results from other studies (Carnethon, Rasmussen-Torvik, & Palaniappan, 2018; Qin, Liu, & Wan, 2017; Conway et al. 2009).

This study found a total of 86% of T1D patients had some level of retinopathy. These findings agree with findings from other studies (Esteves et al. 2009; Roy et al. 2004; Fong et al. 2004).

5.4.Study strengths and limitations

5.4.1. Strengths

The management of T1D is principally carried out in the secondary care, with support from the primary care systems. The use of the Wirral diabetes register, which had linkages between primary, secondary and other allied services allowed for accurate ascertainment of patients with T1D in the Wirral. The use of the register allowed for accurate information to be garnered that aided in the process of disease surveillance, aiding in the estimation of accurate estimates concerning T1D in Wirral which has contributed to existing knowledge, and quality improvements.

The retrospective cohort study design was best fit to establish estimates for time to event analysis; it provided accurate indices for life expectancy, standardised mortality rates, hazard ratios, relative and absolute mortality. This is one of the studies of its kind that has established the impact of several competing risk factors on mortality in T1D. It has highlighted the role and input of several factors such as the age of diagnosis, duration of diabetes, biochemical profiles, and socioeconomic factors such as smoking, and IMD on the survival of individuals with T1D.

One other strength to this study is the use of a large of a number of participants (sample size) who were selected by applying some strict selection criteria; allowing for estimation of precise estimates that allowed drawing inference from predictor variables and mortality. It also aided the exploration of competing risks and their outcome variables in T1D. The systematic review

and meta-analysis on mortality established current trends in mortality and established research gaps which formed the basis for the research questions for this study was conducted.

5.4.2. Limitations of the study

This study had inclusion criteria of T1D diagnosed before the age of 40 years. A potential limitation may have been the inclusion of a small number of participants that may have had the actual diagnosis of T2D. This may have minimally impacted on the precise estimates for relative and absolute mortality.

The inherent design of this study infers that the potential limitations of non-randomisation of participants in this cohort may be present. These include biases such as selection bias, loss to follow-up and confounding. Strict adherence to the inclusion criteria and the use of appropriate statistical techniques were introduced to correct for biases. Additionally the retrospective study design ensured that selection bias was absent.

One major limitation of this study is its inability to access for the causes of death in study participants owing to the inability to acquire the data due to restrictions from the law, the destruction of mortality data after 8 years after death meant that information on the cause of death was no longer available for analysis.

In using internal comparison cohorts for this study ensured that the groups had similar characteristics. However, this allowed for increased probability of type 1 error. This was catered for by using the Bonferroni method, which corrected P-values to ensure statistical significance.

One other limitation of this study is the impact of missing data for the variables used in analyses for the study. The may have potentially reduced the precision of estimates for analysis of the various competing risk on mortality in T1D in the Wirral. However, because the missing values were missing at random, the decisions to include them in the analysis lead to convergence in statistical models analysis. Owing to the sample size, and statistical significance (p-0.05), the impact of the variability of confounding was reduced.

Chapter 6: Conclusion and Recommendations

This study set out to establish the following; current trends in mortality, analysis of the key policies set out during the study period their achievements and recent evidence, establish the competing risk contributing to mortality in T1D within the Wirral, and establish how predictor factors (age at diagnosis, body mass index (BMI), socioeconomic status, age, sex, and duration of T1D, biochemical profiles that include glycaemic control and lipid profiles, and complications) influenced mortality in T1D in the Wirral.

6.1. Contributions from the literature review and systematic reviews

The literature review chapter established the important role of bio-physiological processes leading to the diagnosis of T1D, highlighting complex interactions between genetic and environmental factors involved in the mechanisms that trigger the onset of T1D these mechanisms. Studies that generated evidence as it relates to T1D were mostly derived from epidemiological studies; they identified that the morbidity and mortality that results from the diagnosis of T1D involves an interplay of predictor and competing risk factors that are not necessarily additive but evolve through complex interplays. The systematic review of mortality established recent trends in mortality in T1D.

6.2. Contributions of the findings of this study

In this study, while the incidence of T1D in the Wirral remained relatively stable with a minor decline at the end of the study, there was a steady increase in the prevalence of T1D. This infers that the prevalence of T1D is largely due to improved survival primarily relating to improved management of this condition further evidenced by improving life expectancy from T1D.

Several predictive and competing risk factors in this study are contributory to proportionate levels of mortality in T1D. The complex interplays of these factors majorly contributed to the reduced life expectancy and the negative impacts on survival from T1D. For instance, for absolute and relative risk, gender, age at diagnosis, duration of T1D, BMI, serum creatinine levels, SBP, total cholesterol, LDL, HDL, TC\HDL, and LDL\HDL showed a linear increase in mortality risk. The IMD and DBP followed a U-shaped relationship with relative and absolute mortality, while glycaemic levels reveal a sinusoidal pattern with the highest risk of mortality at the levels $\leq$ 5.9mmol/mol (41%). This study reveals that independently, singular predictor risk factors contribute to relative and absolute mortality in T1D, however when two or more of these predictors risk are combined, the emergent risk of mortality is greatly exaggerated, this risk of mortality is not always linearly exaggerated but mostly follow uncertain and arbitrary outcomes. For example, the combination of smoking, hypertension and lipid abnormalities increases and accelerates the risk of vascular damage resulting in increased risk of macrovascular complication and mortality from cardiovascular conditions (Collier et al. 2018; Schofield et al. 2016; Pan et al. 2015; Weis et al. 2001).

The study found a strong influence of age of diagnosis and duration of T1D on mortality in T1D. It also highlighted that in this cohort, the age-specific relative, absolute and excess mortality in this cohort was higher than the resident comparative population. These findings

reflect that T1D in the Wirral encroach on resources accrued to public health and constitute a significant burden to health resources in the Wirral.

This study established the influence of predictor and competing risk on life expectancy in T1D. This study noted reduced life expectancy in individuals with T1D as compared to those without T1D. At age 40 years, females and males with T1D were expected to live to ages 66 and 78 years respectively as compared to 82 and 78 years for those without T1D in the Wirral. This noted a marked reduction in females as compared to males.

6.3. Contributions to knowledge and implications for practice

This study found the increasing prevalence of T1D puts a burden on the available health resources. Despite, this study has noted significant advancement in the management of T1D over the last 3 decades. This finding translates to infer that advancement in the management of this condition may lead to better management of health resources in the future (Henshaw, 2006; Peckham et al. 2011; Dinesh, 2013).

This study identified significant risk to mortality in those with persistent hypoglycaemic episodes; this risk of mortality was highest in those with average HbA_{1c} levels $\leq$ 5.9% (41mmol/mol). This emphasises the need for healthcare providers to better identify at an early stage and monitor those at risk of recurrent hypoglycaemic episodes with the aim of mitigating the effects of hypoglycaemia (Lachin et al. 2016). This subset of people with increased risk of hypoglycaemic episodes should consider the use of appropriate technology as stipulated by the NICE guidelines. However, the before the institution of these devices are commenced, there is need to establish that the individuals are adequately prepared both physically and psychologically to benefit maximally from the use of CSIIs and CGMs (Lawton et al. 2016).

For this study, the mean ± SD and median ± IQR HbA_{1c} for this cohort were 9.29 ± 20.12 and 8.62 ± 2.00. The mean ± SD and median ± IQR age at diagnosis were 18.37 ± 10.12 and 17.00 ± 15.00. The mean ± SD and median ± IQR duration of T1D were 24.15 ± 15.27and 21.00 ± 22.00 respectively. For this study, the least risk of mortality was for those with HbA1c levels of 6.0-6.4% (42-46mmol/mol). According to targets levels (48 mmol/mol [6.5%]) set by the NICE guidelines, treatment targets should aim for these values. However, it is noted in this study that a significant proportion of participants and extrapolated further that a significant proportion of individuals with T1D still do not attain the recommended target levels set by the NICE guidelines. This supports the argument for an approach of specified individualised approach to care and management to attain target levels as set by the NICE guidelines (Diabetes

UK, 2106). With the mean age of diagnosis being as early as 8 years, there is a need to ensure commencement of individualised care plan at a very early stage of diagnosis after adequate cost-benefit-risk analysis. However, this study acknowledges the availability of limited resources in providing these services.

In this study, a significant proportion of participants had developed some levels of retinopathy, considering the average age of diagnosis for this cohort, it infers that the development of microvascular complications such as retinopathy and nephropathy occur very on early in T1D. Screening services that detect the early onset of these microvascular complications can mitigate further worsening of complications hence improving life expectancy. As such, the recommended process of regular eye examination and the early intervention by laser therapy treatment has significantly reduced the risk of blindness from diabetic retinopathy (Keech et al. 2007; Ciulla, Amador, & Zinman, 2003; Frederick, 1993). This enhances survival and reduces mortality (Jansson, Hufthammer, & Krohn, 2018).

Regardless of the effects that age, gender and muscle mass have on creatinine levels, worsening creatinine levels which translates to worsening GFR leading to diabetic nephropathy remain an early predictor of mortality in T1D. However, the institution of early reno-protective measures such as the use of ACE inhibitors has proven to mitigate the progression of diabetic retinopathy that leads to end-stage renal failure. Similarly, the use of statins has been noted to mitigate the effects of dyslipidaemia leading to the onset and progression of cardiovascular complications (Marcovecchio et al. 2017). However, there remains ongoing argument on how early to institute these measures in T1D soon after diagnosis (Rawshani et al. 2018). Further research is needed on the cost-benefit-risk analysis in beginning these therapies at pre-pubertal or adolescent age in those with T1D.

In this study, while SBP followed a linear relationship with mortality, DBP followed a U-shaped pattern with mortality. This indicates that abnormal high values for SBP and the two extremes of DBP contribute significantly to mortality, this indicates that regular monitoring and control of blood pressures to ensure that within the approved limits as recommended by the NICE guidelines will further reduce the risk of mortality.

This study identified the need for early risk assessments to identify patients who require immediate and ongoing psychological support and institute the appropriate referrals. Also, appropriate support for caregivers (especially parents) through referrals to support groups is essential.

Education stills remain one of the cornerstones to patient empowerment; effort should be made to continue to improve enrolment and participation of patients the approved courses. This would improve better understanding of the management of the condition, hence contributing to the appropriate use of health resources.

6.4. Future research

This study utilised a central database register (WDR), to access data to gather evidence as it relates to mortality indices, including the effects of predictor and competing risk in T1D. However, post-2012 the use of centralised registers have now been decentralised to various subunits. Hence, research that presents a similar picture to this study requires significant effort to gather relevant information. This new system is plagued with different coding systems, and information varies with location. Hence new audit processes are dependent on the response of the individual units which possess the required information. Research is required to estimate the cost-benefit analysis of the two different methods of data storage and access. This research can be explored further by utilising the available ongoing databases such as the Clinical Practice Research Datalink (CPRD), the Health Improvement Network database (THIN), QResearch, and ResearchOne.

Future research is needed to assess factors that affect gender variations that increase the risk of mortality in T1D. Recent advancement in the field of genetics has helped enhance the knowledge of genetic and antibody test that aids in the prevention of T1D or the preservation of insulin function post-diagnosis in T1D. However, this requires further research to scale up these treatment measures. This study has identified that a significant number of patients still do not meet the recommended target levels for HbA_{1c}, future research is needed to explore individualised factors that assist individuals to attain target levels of HbA_{1c}. Further research is needed to assess the advantages of introducing CGMs with insulin pump systems on the management of T1D.

In conclusion, this study has highlighted significant progress in survival and life expectancy over the last 25 years. However, life expectancy from T1D remains sub-optimum as compared to the general population. Mortality risk in T1D is dependent on the several predictors and competing risk; gender variation still exist regarding mortality in T1D.There is need for further understanding of the processes that enhance the complex interplay of the predictor risk factors and the emergent outcomes of T1D.

Word count 59.297

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APPENDICES

Appendix I

Retrospective cohort study of Type 1 Diabetes Mellitus (T1DMM) in the Wirral Peninsula

Background

It is estimated that over 350 million people have been diagnosed with an estimated rise to over 500 million cases in the year 2035 (International Diabetes Federation (IDF), 2014).

Diabetes (DM) is known to be of great public health concern in the United Kingdom (Diabetes UK, 2010). Research indicates that there is an increasing number of people being diagnosed with diabetes has increased from 1.6 million in 1996 to 3.2 million in 2014 (Diabetes UK, 2014). A future of this trend postulates that the number of people that would suffer from this condition in 2025 would be almost 5 million people, at the moment an estimate of about 630,000 people remain undiagnosed (Diabetes UK, 2014; IDF, 2014). The UK currently spends approximately 10% of its annual NHS expenditure which equates to almost 9 billion pounds per year in tackling Diabetes (Diabetes UK, 2014).

Type 1 diabetes (T1DM) a major contributor to the overall prevalence of DM is estimated to be increasing by almost 3% yearly having a total number of approximately 330, 000 cases in the UK (Diabetes UK, 2010). Type 1 Diabetes (T1DM) is considered to be a condition of great health concern as it results in chronicity that is carried on through life for any individual affected. Majority of the cases are attributed to autoimmune in origin, resulting in the destruction of B-cells of the Langerhans islets. Although some cases are also non-autoimmune forms (maturity-onset diabetes of youth- MODY). It is also known that Type 1 Diabetes (T1DM) can considerably reduce the life expectancy of an individual by as much as 20 years (Diabetes UK, 2014).

Critical analysis of the existing literature

T1DM is known to correlate closely with significant risk of acquiring cardiovascular disease (CVD) and increased risk of all-cause mortality (Aanstoot et al. 2007). Cardiovascular disease (CVD) contributes to 44% of fatality in people with type 1 DM (Diabetes UK, 2014). Previous studies demonstrate that good glycaemic control is paramount to potentially reduce the occurrence of CVD and other related DM complications (Orchard et.al. 2006; Liingstone et al. 2012). However, the impact of tight glycaemic control on the relative risk of CVD and mortality in the UK remains uncertain (Soedamah-Muthu et al. 2006). Whilst several studies report CVD incidence among those with T1DM, there are few studies that have directly compared CVD incidence in T1DM with the general population (Soedamah-Muthu et al. 2006).

Contribution to knowledge

There is a need therefore to obtain a comprehensive picture of relative CVD and other morbidity rates (e.g. stroke, amputation, nephropathy, neuropathy, carcinoma) and mortality rates associated with T1DMM.

Method

The method employed for use in this study will be a retrospective (historical) cohort study design using data (2000-2012) from the Wirral Diabetes Register. The retrospective cohort study has the merit of investigating multiple outcomes of a single risk (type 1 DM), it also allows for ease of subgroup analysis within cohorts. This method is appropriate for T1DM due to the temporal sequence between diagnoses and the manifestation of complications. There would also be a comparison with the National UK data in the general population (Nwaneri, Bowen Jones, & Cooper, 2013). The comparison would be set in context using a narrative review of diabetes service provision within the set period.

Rationale and aims

1. To obtain a comprehensive picture of relative CVD and other morbidity rates (e.g. stroke, amputation, nephropathy, neuropathy, carcinoma) and mortality rates associated with T1DM.
2. To obtain a comprehensive picture of service provision (policy documents) between 2000-2014 in England and its application in the Wirral peninsula.
3. Provide information that will impact service utilisation and practice, creating avenues for further research

Methodology

The Wirral Diabetes Register provides data for a cohort of 16,000 people (2012 figures) living with T1DM from 1997 to 2012. It ensures that all patients (≥18 years) are reported yearly based on annual patient visits in primary or secondary care. The data therefore captures a clear temporal sequence of exposure to T1DM, including changes in treatment and service modalities, alongside multiple outcomes related to T1DM. Data are quality assured annually and these data (alongside pre-existing notes) are stored for 8 years following patient mortality. The magnitude, depth and quality of information held on the register offers the prospect of conducting a large retrospective cohort study of T1DM (Appendix 1 for sample of diabetes register form).

Wirral Diabetes Register: summary of data available Demographic factors Diabetes duration Attendance rates to clinic Treatment (and therefore co-morbidities based on treatment profiles) Blood pressure	Biochemical profiles: HbA1c, micro-albuminuria, urea, electrolytes. Lipid values Fundoscopy screening for retinopathy Foot screening for neuropathy Complication rates Referrals to Allied Health Professionals e.g. dietician, chiropodists, psychologists

Table 1: Summary of available data

The study will be divided into five phases:

1. Narrative qualitative analysis of T1DM service provision between 2000-2012 in England and its application in the Wirral peninsula. This would be done using a realist review which brings into focus the practical realities and evidence on health care policies in relation to diabetes care (Pawson, Greenhalgh, Harvey & Walshe, 2005).
2. Current evidence based on quantitative systematic reviews of factors related to T1DM, such as mortality rates; rates of micro- and macro-vascular complications and carcinoma; and sub-group analysis to explore mortality and morbidity in relation to socio-economic factors, age, gender and life style.
3. Statistical analysis of the T1DM Wirral Diabetes Register data including: mortality rates; rates of micro- and macro-vascular complications and carcinoma; and sub-group analysis to explore mortality and morbidity in relation to socio-economic factors, age, gender and life style.
4. Comparison with UK National mortality statistics for the general population.
5. Synthesis and interpretation of the data sets using theory.
6. Application to clinical practice

Analyses of data will potentially provide evidence that would inform service delivery, track any variations in diseases pattern over the years, and provide evidence for future research.

Conduct of the research would be done in three stages;

First stage: This will involve critical and detailed qualitative and quantitative reviews of service provisions which would help identify research questions that need to be answered. It would help in the research design.

Second stage: This stage involves data collection and analysis. Data collection will primarily be obtained from the diabetes register. Data will be collected for the specified period (year 2000 forward). Sample selection will include patients who have been diagnosed with type 1 diabetes and sample size will be gotten based on power calculations and inputs from the statistical advisor. The statistical tools will be used to analyse data is the Statistical Package for Social Sciences (SPSS). Analysis of data will be made in relation to the set objectives of the study. The initial process will involve validating data gotten. Various statistical comparisons will be done using test such as; Mann-Whitney U test (unpaired data to test for differences between comparison groups); Wilcoxon signed-rank test (comparing sets of observations on a single sample); chi-squared test (comparing proportions or percentages in categorical data between groups); Spearman, Kendall rank (determining correlations between groups). Statistical significance will be held at p values of <0.05.

Third Stage: This will involve writing up and dissemination of findings using set procedures as provided by the University of Chester PhD guidelines.

Theory

Complexity Theory will be used to provide a guide to the interpretation of findings. Complexity does justice to the dynamics through which the numerous determinants of diabetes outcomes are inter-related. Previous research into diabetes provided insight into the inadequacy of traditional scientific frameworks, demonstrating the need for one that appreciates T1DM as a complex adaptive system (Cooper, & Geyer, 2008). This novel theoretical approach, alongside the study of a large cohort of people with T1DM, comparison with National statistics and the mapping exercise, represent the original contributions made by this research study. Findings will provide data to inform the development/advancement of current knowledge and recommendations for future research.

ETHICAL CONSIDERATIONS AND RESEARCH GOVERNANCE

In conducting research, it is important to ensure that ethical principles governing the process of research are adhered to (Weingarten, Paul & Leibovici, 2004; The Research Ethics

Guidebook, 2013). In the course of this review, it will be ensured that the work of existing trials will be treated accurately and fairly (The Research Ethics Guidebook, 2013).

Ethical approval may not be explicitly required for this review as it does not directly involve human participation, however the findings of included studies carried out become raw data for analysis and interpretation, it is ethical practice to consider how it can best build on work that has already been done (The Research Ethics Guidebook, 2013; Weingarten, Paul & Leibovici, 2004).

Ethical responsibilities will be taken seriously such as thoroughness in searching, checking of all details and following up on different results, inaccuracies, questionable publication ethics and conflicts of interest (O'Mathuma, 2008). Ethical principles that will be followed during the course of this review are:

Avoidance of harm and distress:

"First, do no harm" is the bedrock of medical ethics, and causing harm should be avoided in any research. The doctrine of "double effect" where an intention for good unintentionally causes harm (Runzheimer & Larsen, 2013) should be kept in mind, as this assist in making difficult decisions about whether actions with double effects can be undertaken. The participants should be made to understand the risk and benefits and which outweighs the other. Avoidance of psychological harm should be avoided when getting information from participants in research; ways should be devised to make participants talk about sensitive issues without making them uncomfortable. Confidential records should be stored securely and specification on how data will be shared should be discussed and specified (Smith, 2003). However, this review involves already published data and these issues do not evolve.

Potential benefits:

Healthcare providers endeavour to improve health, strive to do the most good in every situation or promote good (O'Mathuma, 2008). It involves taking actions to serve the best interest of the subject. Each situation should be considered individually because what is good for one participant may not be for another (Runzheimer & Larsen, 2013). This study is expected to provide stronger precision of estimates, hence provide stronger evidence for public health practice.

Health and Safety issues for researchers:

Responsibility will be taken to work safely and efficiently and not change research protocols for the health and safety of researcher, to ensure that the results of the review are not compromised (Institute of Occupational Safety and Health, 2012). This will be enhanced by following guidelines (Social Research Association, 2013) and scheduled timeline created, feeding and resting adequately to prevent breakdown in health.

Fidelity:

This means experimental manipulations will be conducted as planned or interventions are delivered as designed (Horner, Rew & Torres, 2006) but since there will not be direct contact with participants but results in this review, It will be demonstrated that the review is carried out as planned and each of the outcome components is delivered in a comparable manner to all participants and is true to the theory and goals underlying the research (Dumas, Lynch, Laughlin, Philips & Prinz, 2001).

Justice:

This demands a researcher attempt to be fair as possible when administering the intervention and this action should be justified (Runzheimer & Larsen, 2013). It also involves fair distribution of limited resources (O'Mathuna, 2008). This principle will be adhered to in this review.

Veracity:

In general, truthfulness, accuracy, conveying and perceiving the truth will be done during the course of this review and the report will be conveyed as the study reveals.

Confidentiality and Respect for persons:

This will be adhered strictly to. Identities and research records of participants will be kept confidential whether or not an explicit pledge has been given. The right to remain anonymous and private will be respected and it will be the responsibility of the researcher to protect the confidentiality of participant's data (Social Research Association, 2013).

This study does not require any consent to be gotten, however if need is required to contact anyone this will be gotten and confidentiality kept.

Management of Data:

The Data Protection Act (1998) will be adhered to. The researcher will be accountable to the law; therefore, the use of personal data is bound to comply with this law. These data will be processed fairly and lawfully, efforts will be made to inform participants about any new purposes of data processing or by secondary use by other participants, data only necessary and adequate for the research will be collected and this will be accurate, how long the data will be kept before it is destroyed will be stated and honoured, where necessary data processed will be made available to participants but as long as data do not capture participant's identity this will not be done, steps will be taken to secure personal data and how this will be done will be conveyed to participants, consent will be obtained for any transfer of data; Sensitive data will be processed as duly required (Social Research Association, 2013).

Autonomy:

Participants will have the right to control what happens to them (Runzheimer & Larsen, 2013) or they have the right to decide (O'Mathuna, 2008) and this right of individuals to self-determination will be respected. Furthermore, this review will not involve the participation of vulnerable persons who are persons without the adequate capability to protect them.

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APPENDIX II

AM/bh

7th July 2015

University of Chester

Faculty of Health and Social Care

Akata Eloho
9 Bouverie Street
Chester
CH1 4HF

Tel 01244 512600
Fax 01244 511270

Dear Akata

Ethical Approval Granted

FH&SC Ethics Number:	RESC0515-616
Course of Study:	PhD
Supervisors:	Prof. Helen Cooper, Dr. Andi Mabhala, Prof. David Bowen-Jones
Student Number:	1220994

I am pleased to inform you that the Research Ethics Sub Committee of the Faculty of Health and Social Care approved your project ***"Retrospective cohort study of Type 1 Diabetes Mellitus (T1DMM) in the Wirral Peninsula"*** on 7th July 2015.

Approval is subject to the above and following conditions:

1. That you provide a brief report for the sub-committee on the completion of your project.
2. That you inform the sub-committee of any substantive changes to the project.

We approve your application to go forward to the next stage of the approval process. If you are applying to IRAS and require a sponsorship letter and insurance documentation please contact Barbara Holliday.

If you have any questions or require any further assistance please contact Barbara Holliday on 01244 511117 or by email b.holliday@chester.ac.uk

Yours sincerely

Dr. Andrew Mitchell
Chair, Faculty Research Ethics Sub-Committee

cc Research Knowledge Transfer Office
cc Academic Supervisor

Figure 1: University of Chester Ethical Approval

Appendix III

Wirral University Teaching Hospital NHS

NHS Foundation Trust

Wirral University Teaching Hospital NHS F.T.
Research Department
Elm House
Clatterbridge Hospital
Bebington
Wirral
CH63 4JY

Tel. 0151 678 5111 Ext 5246

21 October 2015

Mr Akata Eloho
9 Bouverie Street
Chester
CH1 4HF
Student number 1220994

Dear Akata Eloho

Study Title	Retrospective cohort study of Type 1 Diabetes Mellitus (T1DMM) in the Wirral Peninsular		
NRES Ref	N/A	**REC Approval Date**	N/A
Name of University	University of Chester		
University Ref	RESC0515-616	**Date of University Ethics Approval**	07 July 2015
R&D Ref	Res Ref 15/034		

I am writing to inform you that you have been granted Trust permission for the above study to be conducted on Trust premises.

Approved Documents	Version	Dated
University of Chester Research application form	1	18/05/2015

Permission is granted on the understanding that the study is conducted in accordance with the Research Governance Framework Good Clinical Practice, Trust Policies and Procedures and all relevant legislation.

As part of research governance this department is required to monitor or audit the progress and outcome of all research within the Trust.

I hope that this study proves to be interesting and rewarding and I would be very grateful to receive a summary upon completion of the project, including, if available, copies of any

publications or presentations. If you have any questions regarding any aspect of research please do not hesitate to contact me.

Yours sincerely

Paula Brassey
Research Manager

CC Professor David Bowen-Jones
Professor Helen Cooper

Figure 2: Ethical Approval from Wirral University Teaching Hospital

Appendix IV

Decision table on The Appropriate Statistical Test (adapted from Intuitive Biostatistics a Nonmathematical Guide to Statistical Thinking Motulsky, 2010).

Goal	Type or level of Data			
	Measurement (from Gaussian Population)	**Rank, Score, or Measurement (from Non-Gaussian Population)**	**Binomial (Two Possible Outcomes)**	**Survival Time**
Describe one group	Mean, SD	Median, interquartile range	Proportion	Kaplan Meier survival curve
Compare one group to a hypothetical value	One-sample t-test	Wilcoxon test	Chi-square or Binomial test **	
Compare two unpaired groups	Unpaired t-test	Mann-Whitney test	Fisher's test (chi-square for large samples)	Log-rank test or Mantel-Haenszel*
Compare two paired groups	Paired t-test	Wilcoxon test	McNemar's test	Conditional proportional hazards regression*
Compare three or more unmatched groups	One-way ANOVA	Kruskal-Wallis test	Chi-square test	Cox proportional hazard regression**
Quantify association between two variables	Pearson correlation	Spearman correlation	Contingency coefficients*	
Predict value from another measured variable	Simple linear regression Or Nonlinear regression	Nonparametric regression*	Simple logistic regression*	Cox proportional hazard regression*
Predict value from several measured or binomial variables	Multiple linear regression* Or Multiple nonlinear regression*		Multiple logistic regression*	Cox proportional hazard regression*

Appendix V

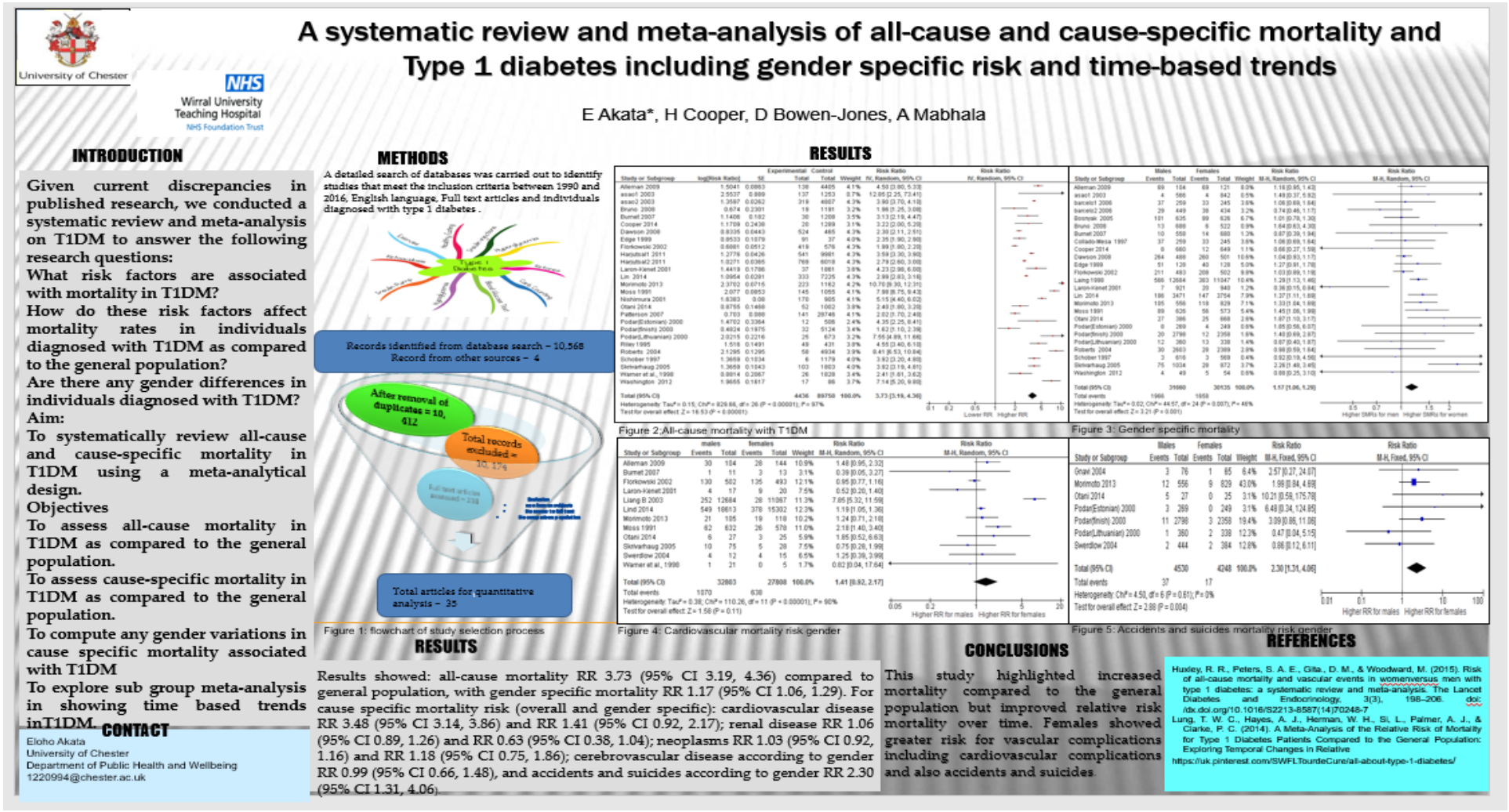

Figure 3: Poster Presentation Diabetes United Kingdom Conference 2017

Appendix VI

Table 3. 3: CASP Checklist

S/N	Author	1	2	3	4	5	6	7	8	9	10	11	12	CASP Score	Follow up period
1	Asao et al. 2003	Y	Y	Y	Y	Y	Y	Y	standardized mortality ratios were 12.9 (10.8–15.3) and 3.7 (3.3–4.1)	N/a	Y	Y	Y	10	25 years.
2	Alleman 2009	Y	Y	Y	Y	Y	Y	Y	Diabetic patients had increased all-cause mortality compared with the general population (SMR [95% CI] 3.8 [3.5–4.3]).	N/a	Y	Y	Y	10	18.8 years
3	Barcelo 2006	Y	Y	Y	Y	Y	Y	Y	Mortality rates higher in HA(14%in males and females, respectively) was higher than in AC (7% in males and 9%in females) for both genders (males, p = 0.0005; females, p = 0.0491)	N/a	Y	Y	Y	10	26 years
4	Bosnyak et al. 2005	Y	Y	Y	Y	Y	Y	Y	Black participants had a significantly higher mortality rate compared with White participants for acute complications (hazard ratio = 4.9, 95%confidence intervals: 2.0, 11.6), but not for any other cause	N/a	Y	Y	Y	10	15.8 years
5	Bruno et al. 2008	Y	Y	Y	Y	Y	Y	Y	The all-cause mortality rate of 1.19/1000 person-years (95% CI 0.76-1.87) and an SMR of 1.96 (1.25-3.08). hazard ratio (HR) (HR=3.90, 95% CI 1.14-13.39)	N/a	Y	Y	Y	10	7.75 years
6	Burnet et al. 2007	Y	Y	Y	Y	Y	Y	Y	Age 17 years (13.36/1,000 person-years), early adolescence (ages 10–13 years) (3.49/1,000person-years), 10 years (0.89/1,000 person-years)or at ages 14–16 years (0.81/1,000 person-years).	N/a	Y	Y	Y	10	17.5 years
7	Collado-Mesa et al. 1997	Y	Y	Y	Y	Y	Y	Y	Overall the cohort experienced 8.5 times all-cause mortality compared to the general populace. Female SMR 10.0 (95% CI 6.9-14.6) higher than Males SMR 7.5 (95% CI 5.3-10.3)	N/a	Y	Y	Y	10	25.6 years
8	Conway 2012	Y	Y	Y	Y	Y	Y	N	HRs (CI) for all-cause mortality was 4.3 (3.4–5.6), 4.2 (2.8–6.3), and 2.0 (1.4–2.8) in groups A, B, and C, respectively.	N/a	Y	Y	Y	9	20 years
9	Cooper 2014	Y	Y	Y	Y	Y	Y	Y	Standardized mortality ratio for all-cause mortality was 1.7 (95% CI 0.7–3.3) for male	N/a	Y	Y	Y	10	6 years

									and 10.1 (95% CI 5.2–17.7) for female subjects with Type 1 diabetes (median age at the end of study 25.6 years).							
10	Dahlquist 2005	Y	Y	Y	Y	Y	CT	Y	Mean age- and sex-SMR was 2.15 (95% CI 1.70 –2.68) and tended to be higher among females (2.65 vs 1.93, P 0.045). Mean age at death was 15.2 years (range 1.2–27.3) and mean duration of 8.2 years (0 –20.7).	N/a	Y	Y	Y	10	15 years
11	Dawson 2008	Y	Y	Y	Y	Y	CT	Y	SMRs were slightly higher for females than males in almost all age-at-onset groups, being 2.48 (95% CI: 2.18–2.78) for females and 2.17 (95% CI: 1.91–2.43) for males overall, but reaching a peak in the <30 age at onset group for both females and males being 4.25 (3.07–5.44) and 3.26 (2.494.03), respectively.	N/a	Y	Y	Y	10	21.4 years
12	Edge 1999	Y	Y	Y	Y	Y	Y	Y	The standardised mortality ratio was 2.3 (95% CI, 1.9 -2.9), being highest in the age group 1–4 years, at 9.2 (95% CI, 5.4 -14.7).	N/a	Y	Y	Y	10	30 years
13	Florkowski 2002	Y	Y	Y	Y	Y	Y	Y	Standardized mortality ratio (SMR) of 2.0 (95% CI 1.8-2.2). Relative mortality was greatest for the group aged 0-29 years (SMR 3.0 (95% CI 2.4-3.7)	N/a	Y	Y	Y	10	10 years
14	Harjutsalo 2011	Y	Y	Y	Y	Y	Y	Y	The all-cause mortality rate of 361 (95% confidence interval 342 to 382) per 100 000 person-years. Standardised mortality ratio was 3.6 (95% confidence interval 3.3 to 3.9) in the early onset cohort and 2.8 (2.6 to 3.0) in the late onset cohort.	N/a	Y	Y	Y	10	37 years
15	Laing 1998	Y	Y	Y	Y	Y	Y	Y	Relative risk of death (standardized mortality ratio, SMR), was higher for females than males at all ages, being 4.0 (95% CI 3.6-4.4) for females and 2.7 (2.5-2.9) for males overall, but reaching a peak of 5.7 (4.7-7.0) in females aged 20-29, and of 4.0 (3.1-5.0) in males aged 40-49.	N/a	Y	Y	Y	10	25 years
16	Laing(a) 2003	Y	Y	Y	Y	Y	Y	Y	The standardised mortality ratios were higher in women than men at all ages, and in women	N/a	Y	Y	Y	9	19 years

									were 44.8 (95%CI 20.5–85.0) at ages 20–29 and 41.6 (26.7–61.9) at ages 30–39.							
17	Laing(b) 2003	Y	Y	Y	Y	Y	Y	Y	1437 deaths during the follow-up, 80 due to cerebrovascular disease. Overall, the cerebrovascular mortality rates in the cohort were higher than the corresponding rates in the general population, and the SMRs were 3.1 (95% CI, 2.2 to 4.3) for men and 4.4 (95% CI, 3.1 to 6.0) for women.	N/a	Y	Y	Y	10	20 years
18	Laron-Kenet 2001	Y	Y	Y	Y	Y	Y	Y	There was significant excess mortality in the patients with Type 1 Diabetes, SMRs being three times higher than that of the general population	N/a	Y	Y	Y	10	31 years
19	Lin 2014	Y	Y	Y	Y	Y	Y	Y	SMR from all-causes were significantly increased at 3.00 (95% Confidence Interval (CI) 2.83–3.16) in patients with T1D. The sex-specific SMR was 2.66 (95% CI 2.46–2.85) and 3.58 (95% CI 3.28–3.87) for male and female patients, respectively	N/a	Y	Y	Y	10	11 years
20	Lind 2014	Y	Y	Y	Y	Y	Y	Y	Corresponding hazard ratios for death from cardiovascular causes were 2.92 (95% CI, 2.07 to 4.13), 3.39 (95% CI, 2.49 to 4.61), 4.44 (95% CI, 3.32 to 5.96), 5.35 (95% CI, 3.94 to 7.26), and 10.46 (95% CI, 7.62 to 14.37).	N/a	Y	Y	Y	10	13 years
21	Moss et al. 1991	Y	Y	Y	Y	Y	CT	Y	The SMR for heart disease was 9.1, with the excess being greater in females (10.3) than in males (8.7).	N/a	Y	Y	Y	10	12 years
22	Morimoto 2013	Y	Y	Y	Y	Y	Y	Y	Mortality rate at the 35-year follow-up (per 100,000 person-years) was 659.3, and the standardised mortality ratio (SMR) was 10.7. The SMR at the 25-year follow-up markedly declined from 19.3 in the 1965–1969 diagnosis group to 6.6 in the 1975–1979 diagnosis group.	N/a	Y	Y	Y	10	35 years
23	Nishimura 2001	Y	Y	Y	Y	Y	Y	Y	Crude mortality rate was 627 per 100,000 person-years (95% CI 532–728), and standardized mortality ratio was 519 (440–602).	N/a	Y	Y	Y	10	34 years

24	Otani 2014	Y	Y	Y	Y	Y	Y	Y	mortality rate (95%CI) and age and sex-adjusted SMR (95%CI) were 457 (288–627) and 3.0 (1.9–4.2) in Group A, 265 (143–387) and 2.2 (1.2–3.2) in Group B, and 144 (29–259) and 1.6 (0.3–2.9) in Group C, respectively	N/a	Y	Y	Y	10	20 years
25	Pambiano 2006	Y	Y	Y	Y	Y	Y	Y	Incidence density per 100 person-years.	N/a	Y	Y	Y	10	50 years
26	Patterson 2007	Y	Y	Y	Y	Y	Y	Y	Standardised mortality ratio (SMR) of 2.0 (95% CI 1.7–2.4).	N/a	Y	Y	Y	10	16 years
27	Podar 2000	Y	Y	Y	Y	Y	Y	Y	The SMR for the Estonian cohort was 4.35 (95% CI 2.25–7.61), the highest for the Lithuanian cohort was 7.55 (4.89–11.15), and the lowest for the Finnish cohort was 1.62 (1.10–2.28).	N/a	Y	Y	Y	10	10 years
28	Raymond 1995	Y	Y	Y	Y	Y	Y	Y	Male and female SMRs were significantly raised for the age groups 45-64, 65-74, and 75-84 years. Cerebrovascular disease accounted for 38 (10%) deaths and the SMR for women was significantly raised.	N/a	Y	Y	Y	10	9 years
29	Riley 1995	Y	Y	Y	Y	Y	Y	Y	Overall SMR of 2.2 (95% CI 2.0-2.4) compared to the Tasmanian population.	N/a	Y	Y	Y	10	9 years
30	Roberts et al., 2004	Y	Y	Y	Y	Y	Y	Y	58 deaths during the three years follow up period (standardised mortality ratio of 8.5; 95% confidence interval 6.5 to 10.8),	N/a	Y	Y	Y	10	31 years
31	Schober 1997	Y	Y	Y	Y	Y	Y	Y	Overall SMR from all causes was 1.53 (95% CI 0.68–3.46) for both sexes and 2.56 (95% CI 0.81–8.12) for females and 1.05 (95% CI 0.33–3.33) for males.	N/a	Y	Y	Y	10	11 years
32	Swerdlow 2003	Y	Y	Y	Y	Y	Y	Y	The SMRs for South Asian patients diagnosed under age 30 years were 3.9 (95%CI 2.0–6.9) in men and 10.1 (5.6–16.6) in women, and in the corresponding non, South Asians were 2.7 (2.6–2.9) and 4.0 (3.6–4.3), respectively.	N/a	Y	Y	Y	10	28 years
33	Skrivarhaug 2005	Y	Y	Y	Y	Y	Y	Y	The mortality rate was 2.2/1000 person-years. The overall SMR was 4.0 (95% CI 3.2–4.8) and was similar for males and females.	N/a	Y	Y	Y	10	20 years

34	Warner et al., 1998	Y	Y	Y	Y	Y	Y	Y	Standardised mortality ratio (SMR) of 247 (95% confidence interval (CI) 163 to 362).	N/a	Y	Y	Y	10	17 years
35	Washington et al., 2012	Y	Y	Y	Y	Y	Y	Y	Overall Mortality rate was 1170 per 100,000 person-years (95% CI: 727, 1883).	N/a	Y	Y	Y	10	40 years